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Synthetic Approaches Towards 2-(4-oxo-4, 5-Dihydro-Thiazol-2-yl) Acetamide

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Abstract: 2-(4-Oxo-4,5-dihydro-thiazol-2-yl) acetamide compound (1), was condensed with aromatic aldehydes either (1:1 molar ratio) or (1:2 molar ratio), and gave the newly 4,5-dihydro- 4-oxo-thiazole derivatives (2a-d), and (3a-c), respectively. Compounds (4a-d) were obtained via cyclocondensation of compound (1), malononitrile, and aromatic aldehydes (1:1:2 molar ratio). Cyclization of compound (2a) with α- substituted cinnamonitriles (6a-d), and (10a-c) yielded the newly thiazolo [3,2-a] pyridine derivatives (9a-d), and (13a-c), respectively.

Key words: 2-(4-Oxo-4,5-dihydro-thiazol-2-yl) acetamide, 4-oxo-thiazoles, thiazolo [3,2-a] pyridines.

1. Introduction

Derivatives of 4, 5-dihydro-4-oxo-thiazoles (Rhod anines) have been prepared and studied as potential antimycobacterial [1], antifungal [2], pesticidal [3], antihypertensive [4]. It was found that they stimulate parathyroid hormone receptor-mediated cAMP formation and could be useful for the local and systemic treatment of rheumatoid arthritis, osteoarthritis and degenerative arthrosis. Enzyme like aldose reductase is not the only inhibited by rhodaninecarboxylic acids. It was found that many other enzymes are inhibited by the derivatives of this structural class [5-9]. In continuation of our interest [11-19] in the synthesis of some novel 4,5- dihydro-4-oxo-thiazoles and thiazlo [3,2-a] pyridines from *2*-(4-oxo-4,5-dihydro-thiazol-2-yl)acetamide (1), we report here the synthesis of some newly 4,5-dihydro-4-oxo-thiazoles and thiazolo [3,2-a] pyridines via the reaction (1), with some deficient centers.

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2. Results and Discussion

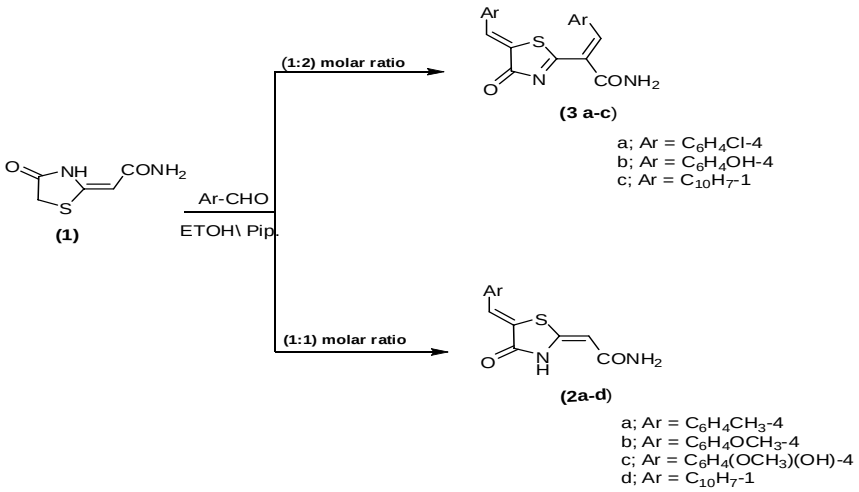
4, 5-Dihydro-4-oxo-thiazole nucleus has been well known in the preparation of some novel thiazolo[3,2-a] pyridine [11] and pyrano[2,3-d]thiazole derivatives [19]. Thus, the work described here started by removal a proton from active methylene moiety of 2-(4-oxo-4, 5-dihydro-thiazol-2-yl) acetamide (1), by using pipe-ridine and formation of thiazolidinone anion which added to deficient centers. On refluxing, compound (1), with aromatic aldehydes(1:1 molar ratio) give the corresponding 4,5-dihydro-4 -oxo-thiazoles (2a-d). The structure of thiazole derivatives (2a-d), was confirmed by correct elemental analysis and spectral data. IR spectra of compounds (2a-d), displayed absorption bands at 3,417, 3,309, 3,380, 3,184, 3,379, 3,147, 3,379, 3,147 cm^{-1} due to amino groups, and at 1,721, 1,647, 1,720, 1,664, 1,720, 1,666, 1,720, and 1,658 cm^{-1} due to presence carbonyl functional groups of the precursor. Their ^1H NMR spectra revealed a lack

of significant signal at δ 3.80 ppm, for methylene protons. The author was interested to synthesize thiazoles containing two arylmethylidine moieties (3a-c), as intermediates compounds between thiazoles having one arylmethylidine moiety and thiazolo[3,2-a] pyridines. Thus, the reaction of compound (1), with aromatic aldehydes (1: 2 molar ratio) in ethanol piperidine solution afforded the newly 2,5-diarylmethylidine- 4,5-dihydro-4-oxo-thiazoles (3a-c). The structure of compounds (3a-c), was confirmed by the correct elemental analysis and spectral data. IR spectra of compounds (3a-c), revealed absorption bands at 3,410, 3,200, 3,432, 3,300, 3,380 and 3,216 cm^{-1} due to amino groups, and at 1,712, 1,648, 1,692, 1,664, 1,704 and 1,648 cm^{-1} as result of carbonyl functional groups of the precursor. Their ^1H NMR spectra showed a lack of signal at δ 3.80 ppm, which attributed to methylene protons (Scheme 1).

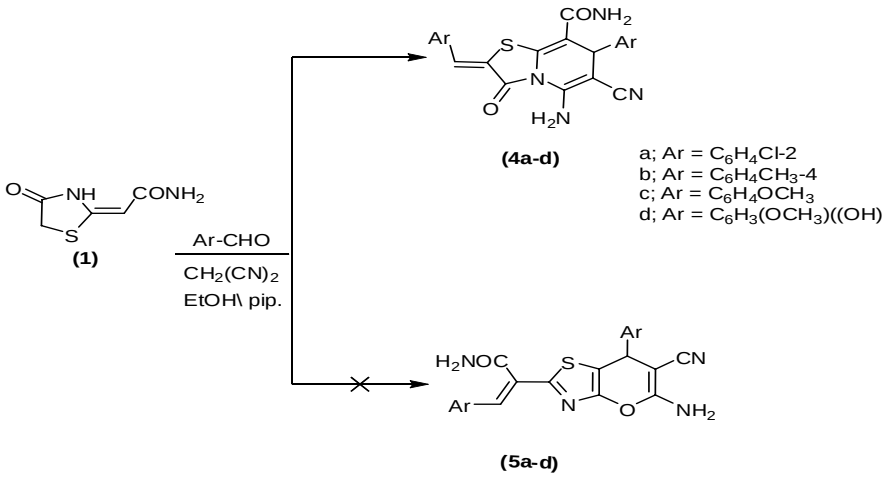
The addition of 2-(4-oxo- 4,5-dihydro-thiazol-2-yl) acetamide (1), to a mixture of malononitrile and aromatic aldehydes (1:1:2 molar ratio) in ethanolic piperidine lead to the formation of an adduct which has two possible structures (4a-d), and (5a-d). However, elemental analyses and spectral data were in complete accordance with the structure of thiazolopyridines (4a-d), and ruled out the other possible structure (5a-d) (Scheme 2). The IR spectrum of compound (4a) was devoid of the absorption bands at 3,480, 3,226, 2,190 and 1,702 cm^{-1} due to an amino, cyano, and carbonyl functional groups, respectively. The ^1H NMR spectra of (4b), showed presence of the characteristic signals for aromatic, methine, and NH_2 protons at δ 6.87-7.61, 4-H pyridine proton at δ 4.71, two methyl protons at δ 2.27, 2.35 ppm (Scheme 2).

The mechanistic equations for formation of compounds (4a-d), can be illustrated in Scheme 3.

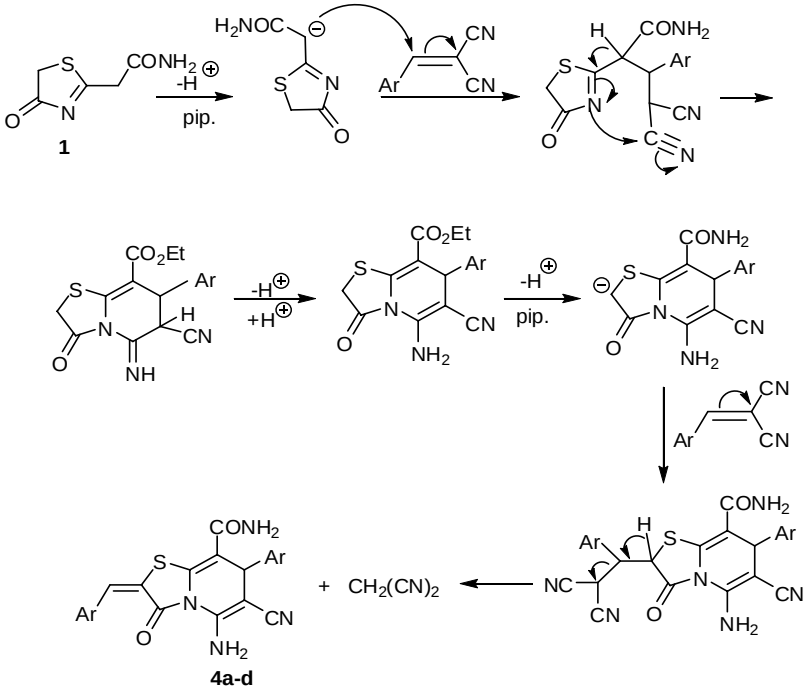
4,5-Dihydro-4-oxo-thiazole (2a), on heating with α-carboxamidocinnamonitrile (6a-d), in ethanolic piperidine solution yield the novel 2,3,6-trihydro-2-arylmethylidine-3-oxo-7-aryl-8-carbo-xamidothiazolo [3,2-a] pyridine-3,5-diones (9a-d), (Scheme 4). Analytical and spectral data are in agreement with thiazolo [3,2-a] pyridine- 3,5- dione structure (9a-d), and the other expected structures thiazolo [3,2-a] pyridines (7a-d), and pyrano [2,3-d] thiazoles (8a-d), were excluded. IR spectrum of the reaction product (9a), showed absorption bands at 3,338, 3,190, 1,686 and 1,654 cm^{-1} due to amino, and two carbonyl functional groups, respectively. The ^1H NMR spectrum of compound (9a), revealed signals at δ 2.37, 5.82, and 8.38 due to methyl, 4 H-pyridine, and amido-NH_2 protons, in addition to a multiplet signal for aromatic and methine protons in the region δ 7.51-8.14



Scheme 1 Synthesis of 4, 5-aihydro-4-oxo-thiazoles.



Scheme 2 Synthesis of thiazol [3,2-a]pyridines.



Scheme 3 Mechanistic equations of thiazolo[3,2-a] pyridine .

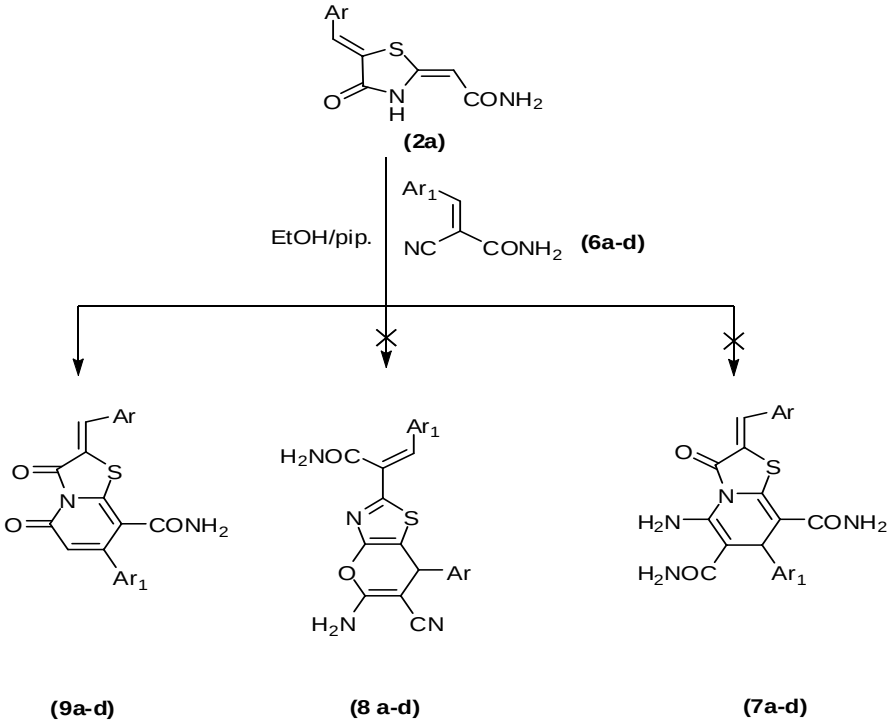
Ppm (Scheme 4). The reaction mechanism for the formation of the novel thiazolo [3,2-a] pyridine-3,5-dione (9a-d), is assumed to proceed via the initial Micheal addition of the thiazolidinone anion to the deficient β-carbon of arylidene (6a-d), to form an intermediate which underwent an intramolecular cyclization followed by elimination of hydrocyanic acid, as in Scheme 5.

A convenient one- step cyclization reaction lead to the synthesis of compounds (13a-c), from 4,5-dihydro-4-oxo- thiazoles (2a), and α-thoxycarbonylcinnamonitrile (10a-c), On the basis of elemental and spectral data the structure of compounds (13a-c), were formulated as thiazolo [3,2-a] pyridines and ruled out the other possible structures (11a-c), and (12a-c), respectively. IR spectra of compounds (13a-c), showed the presence of absorption bands corresponding to NH_2, (C=O amide, ester, and thiazolidinone) functional groups. Also, their ^{1}HNMR data displayed significant signals corresponding to 4H-pyridine. ^{1}HNMR data for (13c), in DMSO-d6 exhibited a strong significant signals, three proton singlet and triplet for two methyl

groups at δ1.34, 2.36, methoxy protons at δ 3.87, one proton singlet for 4 -pyridine-H at δ 4.87, two protons singlet at δ 2.89, 8.21,s for two amino protons, two protons quartet at δ 4.26, for methylene group, in addition to aromatic and methine protons at 7.21-8.10 ppm (Scheme 6).

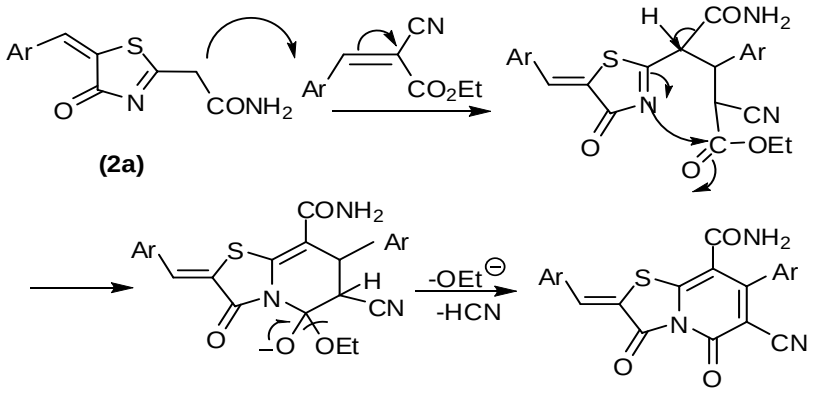
3. Experiment

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^1H NMR spectra were recorded on a Varian Gemini spectrometer (δ; ppm) 200 MHz using TMS as internal standard. Mass spectra were recorded on a Jeol-JMS-600 mass spectrometer. Micro analytical data were obtained from the Micro analytical Research Centre, Faculty of Science, Cairo University. Compound (1), was prepared according to the reported method [19].

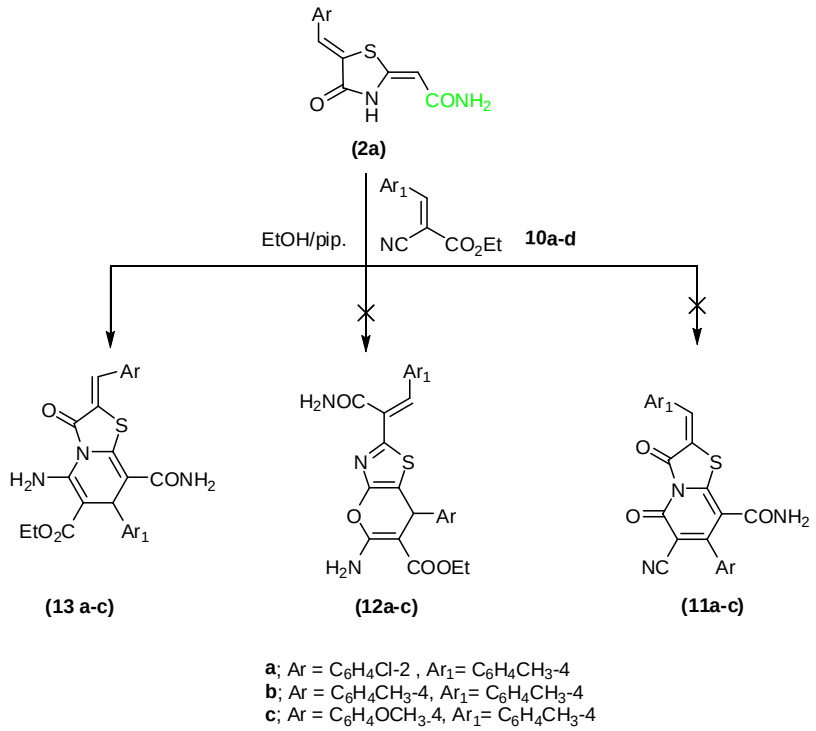


a; Ar= C_6H_4-CH_3 ; Ar_1= C_6H_4Cl-2
b; Ar= C_6H_4-CH_3 ; Ar_1 = $C_6H_4CH_3$-4
c; Ar= C_6H_4-CH_3 ; Ar_1= $C_6H_3(OCH_3)(OH)$-3,4
d; Ar= C_6H_4-CH_3 ; Ar_1= $C_{10}H_7$-1

Scheme 4 Synthesis of thiazolo[3,2-a]pyridinedione.



Scheme 5 Mechanistic equations of thiazolopyridinedione.



Scheme 6 Synthesis of thiazolo[3,2-a]pyridinedione.

3.1 Synthesis of 2- (5-Arylmeth ylidine -4-Oxo thi azolidin-2-Yliden -e) Acetamides (2a-d)

To a solution of 1 (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL), aromatic aldehydes (0.01 mol) were added. The reaction mixture was heated under reflux. The solid products formed were collected by filtration to give 2.

2a. Yellow crystals, yield 67%, m.p. 244-46 ºC (from ethanol). IR (KBr, cm^{-1}): 3,417, 3,309 (-NH_2), 2,923(-CH), and 1,721, 1,674 (-C=O). ^{1}H NMR (DMSO-d_6): 2.41 (s, 3H, CH_3), 5.12 (q, 2H, NH_2, exchangeable with D_2O), 5.63 (d, 1H, methylidene-H), 6.70-7.30 (m, 5H, Ar-H + methylidene-H), 11.22 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{13}H_{12}N_2O_2S$ (260): C, 60.00, H, 4.61; N, 10.76. Found: C, 60.10, H, 4.70; N, 10.60.

2b. Yellow crystals, yield 72%, m.p. 234-36 ºC (from ethanol). IR (KBr, cm^{-1}): 3,380, 3,148 (-NH_2), 2,938(CH-aliph.), and 1,720, 1,664 (-C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6): 4.01 (s, 3H, OCH_3), 5.10 (s, 2H, NH_2, exchangeable with D_2O), 5.51 (s, 1H, methylidene-H), 6.50-7.41 (m, 5H, Ar-H + methylidene-H), 11.10 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{13}H_{12}N_2O_3S$ (276): C, 56.52, H; 4.34; N; 10.14. Found: C, 56.70, H; 4.20, N; 10.10.

2c. Yellow crystals, yield 69%, m.p. 236-38 ºC (from ethanol). IR (KBr, cm^{-1}): 3,379, 3,147 (-NH_2), 2,940(-CH.aliph.), and 1,720, 1,666 (-C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6): 4.01 (s, 3H, OCH_3), 5.11(s, 2H, NH_2, exchangeable with D_2O), 5.51 (s, 1H, methylidene-H), 6.41 (s, 1H, NH, exchangeable with D_2O), 6.81-7.30 (m, 4H, Ar-H + methylidene-H), 11.42 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{13}H_{12}N_2O_4S$ (292): C, 53.42, H; 4.10; N; 9.58. Found: C, 53.50, H; 4.20, N; 9.70.

2d. Yellow crystals, yield 69%, m.p. 238-40 ºC (from ethanol). IR (KBr, cm^{-1}): 3,379, 3,147 (-NH_2), 2,931(CH.aliph.), and 1,720, 1,658 (-C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6): δ 5.02(s, 2H, NH_2, exchangeable with D_2O), 5.30 (s, 1H, methylidene-H), 6.70-7.80 (m, 8H, Ar-H + methylidene-H), 11.21 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{16}H_{12}N_2O_2S$ (296): C, 64.86, H;

4.05; N; 9.45. Found: C, 65.10, H; 4.20, N; 9.20.

3.2 Synthesis of 5-Arylmethylidine -4-oxo -4,5 –Dihydro-Thiazol-2-yl)- 3-Aryl Acrylamides (3a-c)

To a solution of 1 (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL), aromatic aldehydes (0.02 mol) were added. The reaction mixture was heated under reflux. The solid products formed were collected by filtration to give 3.

3a. Yellow crystals, yield 74%, m.p. 225-27 ºC (from ethanol). IR (KBr, cm^{-1}): 3,410, 3,200 (-NH_2), 3,040(-CH-arom.), and 1,712, 1,648 (-C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6): δ 5.98 (s, 1H, methylidene-H), 6.90 -7.68 (m, 9H, Ar-H+, methylidene-H), 8.91 (hump, 2H, NH_2, exchangeable with D_2O), Anal. Calcd for $C_{19}H_{12}Cl_2N_2O_2S$ (403): C, 56.57, H; 2.97; N; 6.94. Found: C, 56.50, H; 2.90, N; 7.10.

3b. Yellow crystals, yield 64%, m.p. 235-37 ºC (from ethanol). IR (KBr, cm^{-1}): 3,432, 3,300 (-NH_2), 3,050 (-CH-arom.), 1,692, 1,664 (-C =O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ 5.78 (s, 1H, methylidene-H), 6.87 -7.50 (2d, 8H, Ar-H), 7.36 (S, 1H, methylidene-H), 10.14 (hump, 2H, NH_2, exchangeable with D_2O), 11.76 (hump, 2H, 2 OH, exchangeable with D_2O). Anal. Calcd for $C_{19}H_{14}N_2O_4S$ (366): C, 62.29, H; 3.82; N; 7.65. Found: C, 62.00, H; 3.70, N; 7.40.

3c. Yellow crystals, yield 65%, m.p. 180-82ºC (from ethanol). IR (KBr, cm^{-1}): 3,380, 3,216 (-NH_2), 3,052 (-CH-arom.), 1,704, 1,648 (-C=O thiazolinone, amide). ^{1}H NMR (DMSO-d_6): δ 5.80 (s, 1H, methylidene-H), 7.58-8.05 (m, 15H, Ar-H + methylidene-H), 9.00 (hump, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{27}H_{18}N_2O_2S$ (434): C, 74.65, H; 4.14; N; 6.45. Found: C, 74.80, H; 4.10, N; 6.60.

3.3 Synthesis of 2,3,7-Trihydro-2-Arylmethylidine-3-oxo-5-Amino-6-Cyano -7-Aryl-8-Carboxamido-1, 3 -Thiazol o[3,2-a] Pyridines (4a-d)

To a solution of 1 (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL), aromatic aldehydes (0.02 mol), and malononitrile (0.02 mol) were added. The reaction mixture was heated under reflux. The solid products formed were collected by filtration to give 4.

4a. Yellow crystals, yield 56%, m.p. 250-52 ºC (from ethanol). IR (KBr, cm^{-1}): 3,480, 3,296 (-NH_2), 2,190 (-C≡N), 1,702 (-C=O thiazol-idinone, amide). ^{1}H NMR (DMSO-d_6): δ 4.72 (s, 1H, pyridine-H), 7.06-7.56 (m, 13H, Ar-H + methylidene-H+ 2 NH_2; exchangeable with D_2O). Anal. Calcd for $C_{22}H_{14}Cl_2N_4O_2S$ (469): C, 56.28, H; 3.01; N; 11.94. Found: C, 56.60, H; 2.90, N; 12.10.

4b. Yellow crystals, yield 61%, m.p. 262-64 ºC (from ethanol). IR (KBr, cm^{-1}): 3,471, 3,379 (-NH_2), 2,191 (-C≡N), 1,674 (-C=O thiazolidi- none, amide). ^{1}H NMR (DMSO-d_6): δ 2.27, 2.35 (2s, 6H, 2 CH_3), 4.71 (s, 1H, pyridine-H), 5.59 (s, 1H, NH, exchangeable with D_2O), 6.87 (hump, 2H, NH_2; exchangeable with D_2O) , 6.91-7.61 (m, 9H, Ar-H + methylidene-H), 12.11 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{24}H_{20}$ N_4O_2S (428): C, 67.28, H; 4.67; N; 13.08. Found: C, 67.30, H; 4.50, N; 13.20.

4c. Yellow crystals, yield 70%, m.p. 258-60 ºC (from ethanol). IR (KBr, cm^{-1}): 3,480, 3,380 (-NH_2), 2,190 (-C≡N), 1,708 (-C=O thiaz- olidinone, amide). ^{1}H NMR (DMSO-d_6): δ 3.74, 3.80 (2s, 6H, 2 OCH_3), 5.91 (s, 1H, pyridine-H), 5.84 (s, 1H, NH, exchangeable- with D_2O), 6.98 (hump, 2H, NH_2; exchangeable with D_2O), 7.34-7.81 (m, 9H, Ar-H + methylidene-H), 12.00 (s, 1H, OH, exchang eable with D_2O). Anal. Calcd for $C_{24}H_{20}$ N_4O_4S (460): C, 62.60, H; 4.34; N; 12.17. Found: C, 62.10, H; 4.10, N; 12.10.

4d. Yellow crystals, yield 52%, m.p. 260-62 ºC (from ethanol). IR (KBr, cm^{-1}): 3,476, 3,358 (-NH_2), 2,191 (-C≡N), 1,686 (-C=O thiazolid -inone, amide). ^{1}H NMR (DMSO-d_6): 3.83, 3.85 (2s, 6H, 2 OCH_3), 4.60 (s, 1H, pyridine-H), 5.76(s, 2H, NH_2, exchangeable with D_2O), 6.83-7.43 (m, 9H, Ar-H + methylidene-H + NH_2; exchangeable with D_2O), 11.80 (2s, 2H, OH, exchangeable with D_2O). Anal. Calcd for $C_{24}H_{20}$ N_4O_6S (492): C, 58.53, H; 4.06; N; 11.38.

Found: C, 58.30, H; 4.10, N; 11.70.

3.4 Synthesis of 2,3,6-Trihydro-2-Arylmethylidine-3,5-Dioxo-7- Aryl -8-Carboxamido- 1,3-Thiazolo- [3,2 -a] Pyridines (9a-d)

To a solution of 2a (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL), α-carboxamidocinnamonitrile (0.01 mol), was added. The reaction mixture was heated under reflux. The solid products formed were collected by filtration to give 9.

9a. Yellow crystals, yield 63%, m.p. 275-77 ºC (from ethanol). IR (KBr, cm^{-1}): 3,338, 3,190 (-NH_2), 3,050 (-CH-arom.), 2,910(-CH-aliph.), 1,686, 1,654 (-C = O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 5.82 (s, 1H, pyridine-H), 7.51-8.14 (m, 9H, Ar-H + methylidene-H), 8.38 (s, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{22}H_{15}ClN_2O_3S$ (422.5): C, 62.48, H; 3.55; N; 62.60. Found: C, 58.30, H; 3.70, N; 6.80.

9b. Yellow crystals, yield 57%, m.p. 292-94 ºC (from ethanol). IR (KBr, cm^{-1}): 3,386, 3,170 (-NH_2), 3,026 (-CH-arom.), 2,922 (-CH-aliph.), 1,696, 1,640 (-C =O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ 2.29, 2.38 (2s, 6H, $2CH_3$), 5.78 (s, 1H, pyridine-H), 7.20-7.60 (m, 9H, Ar-H + methylidene-H), 8.01 (s, 1H, NH, exchangeable with D_2O), 10.31 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{23}H_{18}ClN_2O_3S$ (402): C, 68.65, H; 4.47; N; 6.96. Found: C, 68.50, H; 4.70, N; 6.80.

9c. Yellow crystals, yield 63%, m.p. 290-92 ºC (from ethanol). IR (KBr, cm^{-1}): 3,312, 3,184 (-NH_2), 3,030 (-CH-arom.), 2,928 (-CH-aliph.), 1,684, 1,654 (-C =O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3) 5.78 (s, 1H, pyridine-H), 6.94-7.51 (m, 8H, Ar-H + methyllidene-H), 8.59 (s, 2H, NH_2, exchangeable with D_2O), 10.31 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{23}H_{18}N_2O_5S$ (434): C, 63.59, H; 4.14; N; 6.45. Found: C, 63.60, H; 3.99, N; 6.80.

9d. Yellow crystals, yield 61%, m.p. >300 ºC (from ethanol). IR (KBr, cm^{-1}): 3,450, 3,174 (-NH_2), 3,048 (-CH-arom.), 2,930 (-CH-aliph.), 1,686, 1,654 (-C = O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 5.94 (s, 1H, pyridine-H), 7.35-8.31 (m, 12H, Ar-H + methylidene-H), 10.40 (s, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{26}H_{18}N_2O_3S$ (438): C, 71.23, H; 4.10; N; 6.39. Found: C, 71.00, H; 4.20, N; 6.50.

3.5 2,3,7-Trihydro-2-arylmethylidine-3-oxo-5- amino-6-ethoxycarbonyl-7-aryl-8-carboximido-1,3-thiazolo [3,2-a]pyridines(13a-c)

To a solution of 2a (0.01 mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL), α-ethoxycarbontlcinnamonitrile (0.01 mol), was added. The reaction mixture was heated under reflux. The solid products formed were collected by filtration to give 13.

13a. Yellow crystals, yield 54%, m.p.258-60 ºC (from ethanol). IR (KBr, cm^{-1}): 3,330, 3,196 (-NH_2), 2,980 (-CH-aliph.), 1,710, 1,654 (-C =O thiazolidinone, amide, ester). ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.90 (s, 2H, NH_2, exchangeable with D_2O), 4.31 (q, 2H, CH_2), 4.94 (s, 1H, pyridine-H), 7.20-8.09 (m, 9 H, Ar-H + methylidene-H), 8.41 (s, 2H, NH_2, exchange- able with D_2O). Anal. Calcd for $C_{25}H_{22}ClN_3O_4S$ (495.5): C, 60.54, H; 4.43; N; 8.47. Found: C, 60.70, H; 4.60, N; 8.30.

13b. Yellow crystals, yield 72%, m.p.180-82 ºC (from ethanol). IR (KBr, cm^{-1}): 3,330, 3,196 (-NH_2), 2,980 (-CH-aliph.), 1,710, 1,654 (-C =O thiazolidinone, amide, ester). ^{1}H NMR (DMSO-d_6): δ 1.33 (t, 3H, CH_3), 2.29, 2.38 (2s, 6H, CH_3), 2.89 (s, 2H, NH_2, exchangeable with D_2O), 4.31 (q, 2H, CH_2), 4.94 (s, 1H, pyridine-H), 7.16-7.98 (m, 9 H, Ar-H + methylidene-H), 8.34 (s, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{26}H_{25}N_3O_4S$ (475): C, 65.68, H; 5.26; N; 8.84. Found: C, 65.90, H; 5.10, N; 8.80.

13c. Yellow crystals, yield 79%, m.p.195-97 ºC (from ethanol). IR (KBr, cm^{-1}): 3,370, 3,184 (-NH_2), 2,930 (CH-aliph.), 1,702, 1,656 (-C =O thiazolidinone,

amide, ester). ^{1}H NMR (DMSO-d_6): δ 1.34 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.89 (s, 2H, NH_2, exchangeable with D_2O), 3.87 (s, 3H, OCH_3), 4.26 (q, 2H, CH_2), 4.87 (s, 1H, pyridine-H), 7.12-8.10 (m, 9 H, Ar-H + methylidene-H), 8.34 (s, 2H, NH_2, exchange- able with D_2O). Anal. Calcd for $C_{26}H_{25}N_3O_5S$ (491): C, 63.54, H; 5.09; N; 8.55. Found: C, 63.40, H; 5.20, N; 8.40.

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