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SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL THIAZOLE, THIAZOLO[3,2-A]PYRIDINE AND THIAZOLO[3,2-A]-1,8-NAPHTHYRIDINE DERIVATIVES CONTAINING MORPHOLINE MOIETY

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Abstract

One pot reaction of morpholin or piperidine , ethyl cyanoactate,and thioglycollic acid afforded the novel 2-(2-morpholino-2-oxo-ethylidene)-4-thiazolidinone and 2-(2-oxo-2-(piperidin-1-yl) ethylidene) thiazolidin-4-one **(1a,b)**.Cyclization of **(1a)** with chloroacetonitrile and malononitrile afforded the novel thiazolidinone derivatives **(2a,b)**.Refluxing of **(1a)** with o-chlorobenzaldehyde,and chloroacetonitrile furnished **(3)**. Compound **(1a)** reacted with aromatic aldehydes in refluxing ethanol affording 5-arylmethylidine-4-thiazolidinone **(4a,b)**.4-Thiazolidinone derivative **(4a**) was cond-ensed with hydrazine hydrate to give **(5)**. Thiazolo [3,2-a]pyridine and pyrano [2,3-d]thiazole derivatives **(6,7)** were produced through reaction of **(4a,b,)** with a mixture aromatic aldehyde and malononitrile. Compound **(6)** was reacted with ethyl isot-hiocynate and hydrazine hydrate to give the corresponding thiazolopyridine derivatives **(8,9**) .When compound **(6)** was treated with each of HCOOH, C_6H_5CO Cl,,and CS_2 and malononitrile , the novel thiazolo [3,2-a]-1,8-naphthyridine derivati -ves **(10-13**) were obtained.

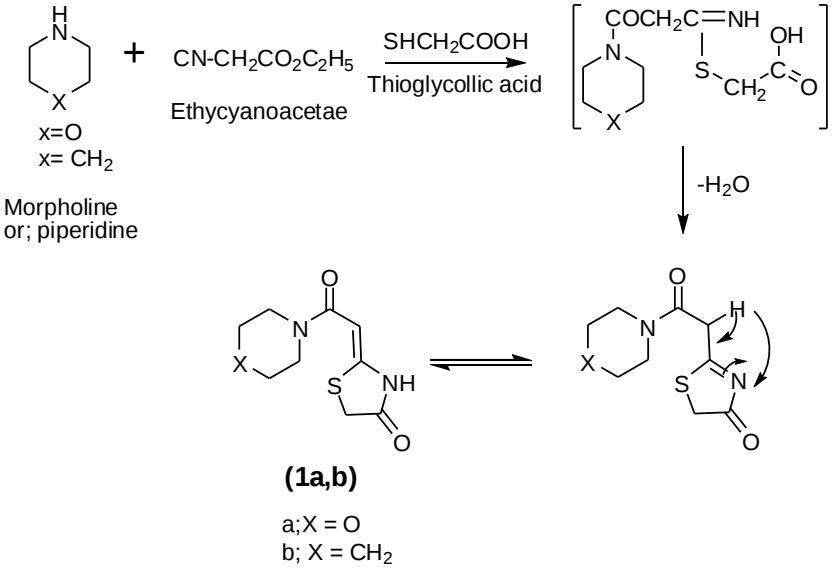
Key words:, Thiazolo[3,2-a] pyridine , thiazolo[4,5-c] pyrazole, and thiazolo[3,2-a]-1,8-naphtharyidine derivatives

I**ntroduction**

Thiazoles are important class in heterocyclic compounds, found in many potent biological active molecules such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral), Abafungin (antifungal drug) and Bleomycine (antineoplastic drug).[1,2] Recently the applications of thiazoles were found in drug development for the treatment of allergies,[3] hypertension,[4] and inflammation.[5] Morpholine derivatives have been reported to possess antimicrobial,[6] hypoglycemic,[7] antagonists of leukocyte,[8] tyrosine kinas inhibitory,[9] and inhibition of collagen-induced blood aggregation.[10] Thus, in conjunction to our interest in developing syntheses for biologically interesting thiazolo[3,2-a] pyridines,[11-17] we disclose a new synthesized, thiazolo[3,2-a] pyridine ,pyrazolo [3,4-d] thiazole, and thiazolo [3,2-a]-1,8-naphthyridine, derivatives bearing a morpholine moiety to improve their antimicrobial activities.

Results and Discussion

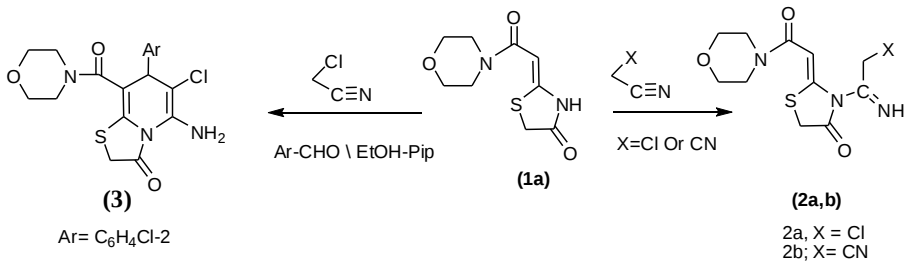
The starting 2-(2-morpholino-2-oxo-ethylidene)-4-thiazolidinone and 2-(2-oxo-2-(piperidin-1-yl) ethylidene)thiazolidin-4-one **(1a,b)** were easily prepared in one pot reaction from the corresponding ethyl cyanoacetate , thioglycollic acid, and morpholine or piperidine. The IR spectrum of thiazolidin-4-one **(1a)** showed absorption bands at 3276,1724, and 1660 cm^{-1} due to NH ,and (C=O thiazolidinone, and amide) functional groups, respectively. Moreover, the mass spectra of the isolated products **(1a,b)** revealed a molecular ion peaks at *m/z* (228) and (226); respectively (Scheme 1).



Scheme (1): 2-(2-morpholino-2-oxo-ethylidene)-4-thiazolidinone and 2-(2-oxo-2-(piperidin-1-yl) ethylidene) thiazolidin-4-one (1a,b)

Treatment of 2-(2-morpholino-2-oxo-ethylidene)-4-thiazolidinone **(1a)** with either chloroacetonitrile and or malononitrile in refluxing ethanol containing catalytic amount of pipridine furnished the product**s (2a,b)**, respectively . However, elemental analyses and spectral data were in acomplete accordance with the thiazolidinone derivatives (**2a,b)**. The IR spectra of the reaction products showed absorption bands at 3252, 3210, 1716 and 1710cm^{-1} due to NH, and two(C=O thiazolidinone) groups, respectively. Moreover, the mass spectrum of the isolated products revealed a molecular ion peak at *m/z* (301) and (292). ^{1}H zNMR spectrum of compound (**2b)** revealed signals at δ 3.33,3.77, 5.43,and 5.87

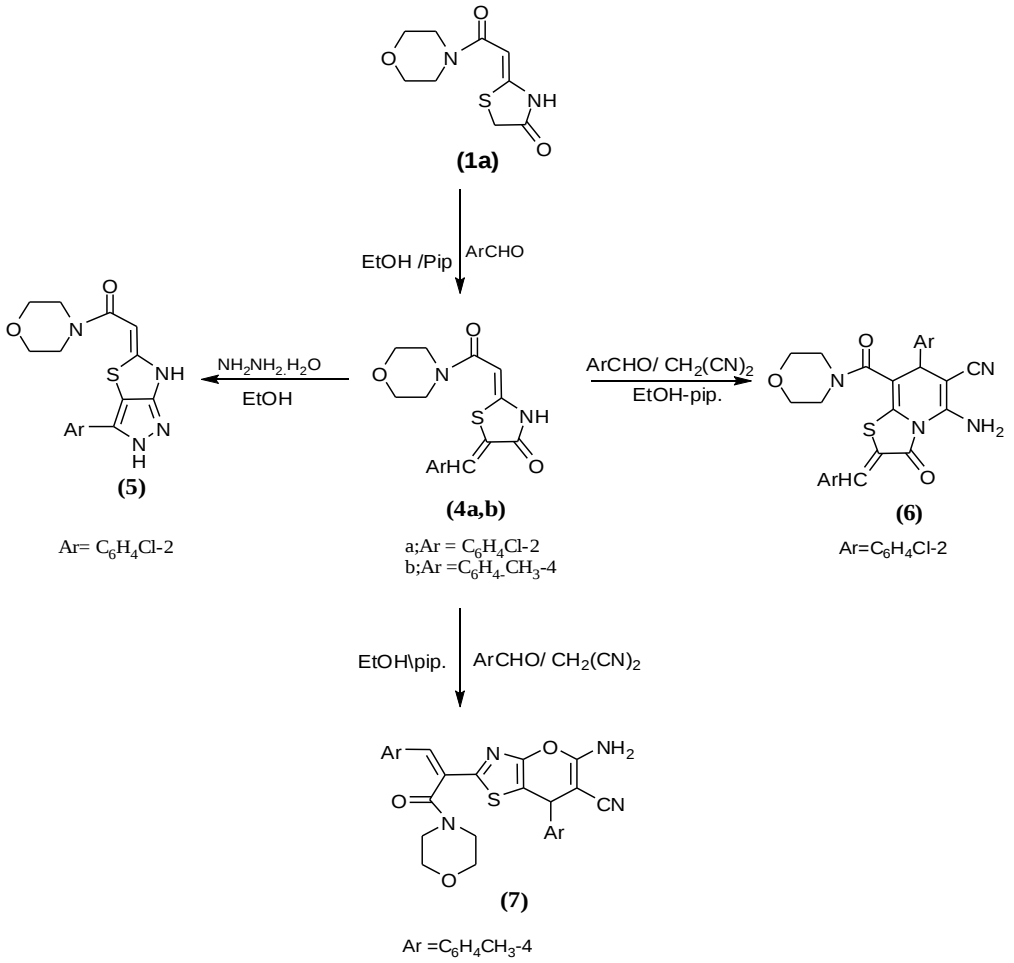
due to morpholine, NH and methine, protons. One pot reaction of the 4-oxo-thiazolidine (**1a)** with 2-chlorobenzaldehyde and chloroacetonitrile in refluxing ethanol afforded one isolable product which was analyzed correctly for $C_{18}H_{17}Cl_2N_3O_3S$. The structure of the isolated product was assigned as 2,3,7-trihydro-3-oxo-5-amino-6-chloro-7-(2-chlorophenyl)-8-(morpholine carboxamide) thiazolo [3,2-a]pyridine (**3**) based on its elemental analyses and spectral data. Its IR spectrum revealed presence of amino and (C=O thiazolidinone) absorption bands at 3252, 3078 and 1712cm^{-1}; (Scheme 2)



Scheme (2): Synthesis of 4-thiazolidinone ,and thiazolo[3,2-a]pyridine derivatives (2a,b) and (3).

Also, compound (**1a)** was condensed with aromatic aldehydes in refluxing ethanol having catalytic amount of piperidine and afforded thiazolidinones **(4a,b).** Spectral data were in agreement with thiazolidinone structure **(4a,b)**. The mass spectrum of the isolated product **(4a)** revealed a molecular ion peak at *m/z* 350 and, where as ^{1}H NMR spectrum of compound (**4b)** revealed specific signals at δ 2.35, 3.33, 3.77, and 5.44 due to methyl, morpholine, and NH protons. Next, the reaction of 4-thiazolidinone **(4a)** with hydrazine hydrate in refluxing absolute ethanol afforded a single product as examined by TLC. The structure of the isolated product was assigned as 2-(3-(2-chlorophenyl)-2H-pyrazolo [3,4-d] thiazol-5(6H)-ylidene)-1-morpholino ethan-one **(5)**, on the basis its elemental analyses and spectral data. The IR spectrum of compound (**5)** was free of C=O thiazolidinone absorption band and showed presence of absorption band at 3178 cm^{-1} for NH group, in addition, its ^{1}H NMR spectrum was in a complete agreement with the assigned structure, (Scheme 3). Compound **(4a)** was reacted with a mixture of 2-chlorobe-nzaldehyde and malononitrile in refluxing ethanol to give 2,3,7-trihydro-2-arylmethylidine-3-oxo-5-amino-6-cyano-7-aryl-8-(morpholino-4-carbonyl) th-iazolo [3,2-a] pyri-dine **(6)** in 82% yield; Whereas the novel 3-(p-tolyl)- 4 -cyano-5-amino-8-(morpholine-carboxamide) pyrano [2,3-d] thiazole **(7)** was isolated in 67% yield identified on the

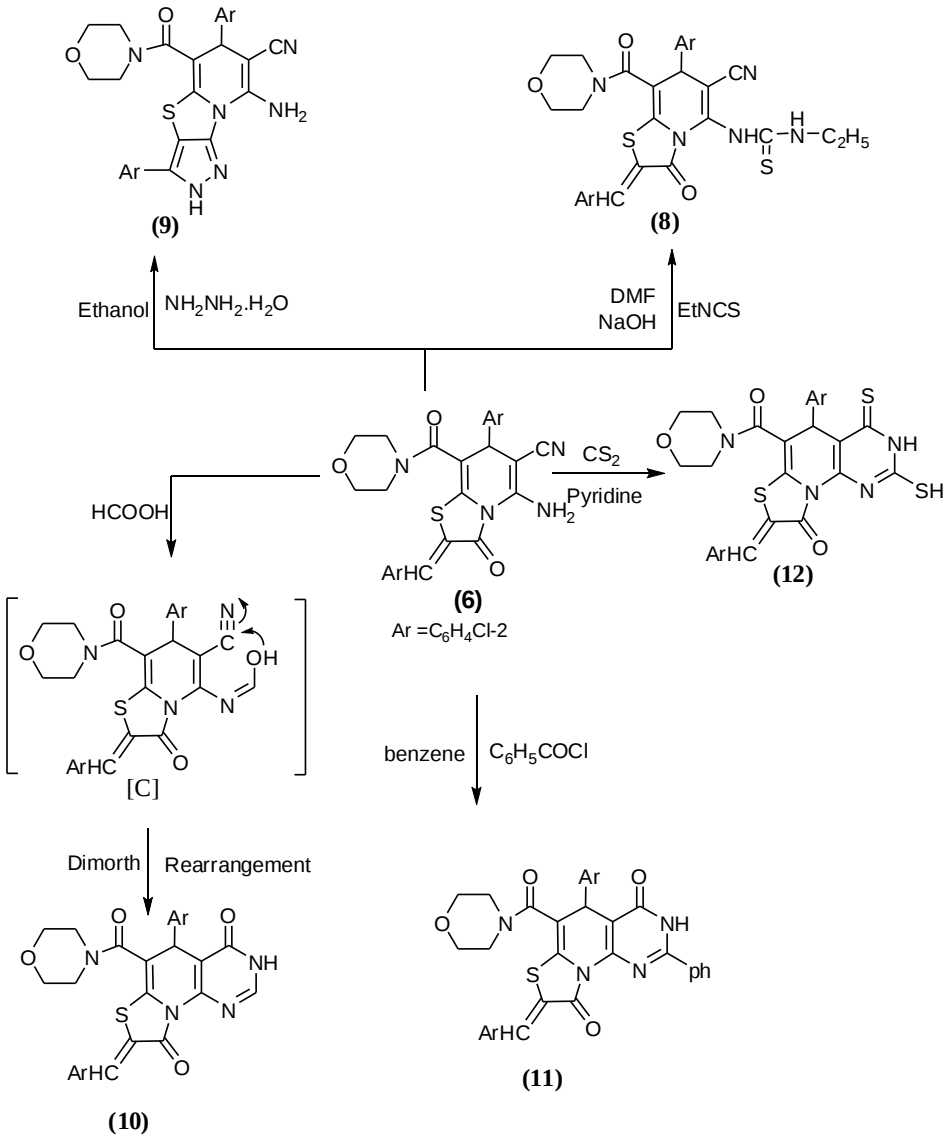
basis of their spectral analyses, when compound **(4b)** was treated with a mixture of p-tolualdehyde and malon-onitrile; Mass spectra of thiazolo[3,2-a] pyridine and pyrano [2,3-d] thiazole derivatives **(6,7)** assigned a molecular ion peaks at m\ z 427 (M^+- C_6H_4Cl) and 498; respectively (Scheme 3)



Scheme (3): Synthesis of pyrazolo [3,4-d]thiazole , thiazolo[3,2-a]pyridine, and pyra-no [2,3-d] thiazolo derivatives (5),(6), and (7)

The reactivity of the thiazolo [3,2-a] pyridine **(6)** as nucleophile towards ethylisothiocynate as electrophile in DMF in presence of NaOH, afforded the novel

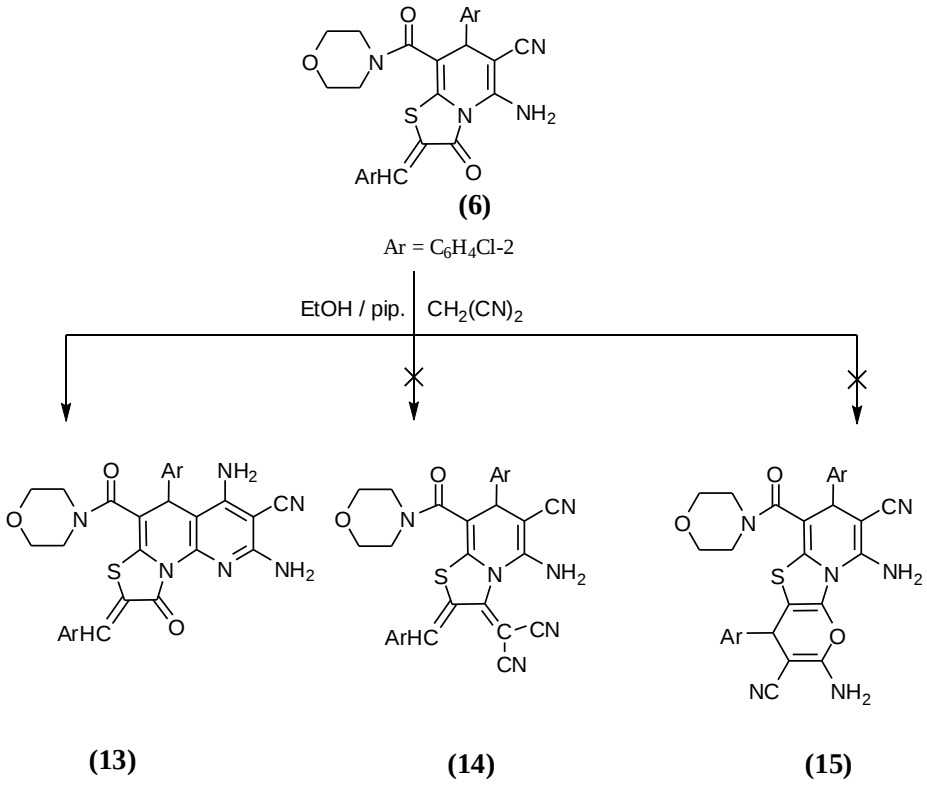
thiazolopyridine derivative (**8**). The structure of compound (**8**) was confirmed by its correct elemental and spectral data. The IR spectrum of compound **(8)** revealed presence of absorption bands for NH, cyano and carbonyl functional groups at 3326, 2198,1702,and 1628 cm^{-1} , in addition, its ^{1}H NMR spectrum was in a complete agreement with the assigned structure ; (Scheme 4). The reactivity of the thiazolo [3,2-a] pyridine **(6)** towards hydrazine hydrate[12] in refluxing ethanol was also investigated. A single product as examined by TLC was produced. The structure of the obtained product was assigned as 3,9-(2-chlorophenyl)-7-amino-8-cyano-10-(morpho-line-carboxamide) pyrazolo[3,4-d] thiazolo [3, 2-a] pyridine **(9**); (Scheme 4), based on its elemental analysis and spectral data. IR spectrum of (**9)** was free of C=O thiazolidinone absorption bands in the region 1690-1712cm^{-1} .Its^{1}H NMR showed significant signals at 3.33, 3.60, and 4.14 for morpholinyl, and pyridinyl protons. In conjunction with the interest in the chemistry and biological activity of polycondensed thiazolopyridines, thiazolo[3,2-a]pyridine derivative **(6)** was reacted with each of formic acid , benzoyl chloride and carbon disulphide to give the corresponding polycondensed thiazolo [3,2-a]-3-aza-1,8-naphthyridine derivatives **(10**-**12**), respectively. The structure of the latter products was deduced from their elemental analyses and spectral data. IR spectra of thiazolo[3,2-a]-3-aza-1,8-naphthyridines **(10**-**12**) was free of cyano absorption bands in the region 2000-2200 cm^{-1} .^{1}H NMR spectra of thiazolo[3,2-a]-3-aza-1,8-naphthyridines showed significant signals for morpholine moiety and pyridine-H; (Scheme 4)



Scheme (4): Synthesis of thiazolo[3,2-a]pyridine and thiazolo[3,2-a] -3-aza-1,8-naphthyridine derivatives (8,9), and (10-12).

Compound (**13**) was synthesized via the reaction of thiazolo [3,2-a] pyridine derivative **(6)** with malononitrile in refluxing ethanol containing a catalytic amount of piperidine. Spectral and elemental analysis were in a complete accordance with thiazolo[3,2-a]-1,8-naphthyridine structure **(13)** and ruled out the

other possible structures **(14)**, and **(15)**. IR spectrum of (**13)** showed C=O thiazolidinone absorption band at 1719 cm^{-1}.Its ^1H NMR showed significant signals at 3.33,3.59, and 5.10 for morpholinyl, and pyridinyl prot-ons; Scheme (5)



Scheme (5): Synthesis of thiazolo [3,2-a]-1,8-naphthyridine derivative (13).

Experimental

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^{1}HNMR 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.

2-(2-morpholino-2-oxoethylidine)-thiazolidine-4-one and 2(2-oxo-2-(piperiridin - 1-yl)ethylidene)thiazolidin-4-one (1a,b).

A mixture of morpholine or piperidine (0.01mol), ethylcyanoacetae (0.01mol), and thioglycollic acid (0.01mol) in absolute ethanol (20 mL) was heated under reflux for 2h. The solid product formed was collected by filtration and recrystallised from ethanol.

1a: colorless crystals, yield 72 %, m.p. 187-89 ºC. IR (KBr, cm^{-1}): 3276 (NH), and 1724, and 1660 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 3.33 (s, 4H, $2CH_2$-mor), 3.77 (s, 4H, $2CH_2$-mor), 4.21(s, 2H, CH_2- thiazolidinone), 5.43 (s, 1H, NH, exchangeable with D_2O) 6.72 (s,1H, methine-H),). MS m/z (%): 228 (M^+, 27.82) .Anal. Calcd for $C_9H_{12}N_2O_3S$ (228): C; 47.35, H; 5.30; N; 12.27. Found: C; 47.75, H; 5.10, N; 12.40.

1b: colorless crystals, yield 82 %, m.p. 154-56 ºC. IR (KBr, cm^{-1}):3252 (NH), 1724, and 1660 (C=O thiazolidinone and amide). MS m/z (%): 226 (M^+,19.26) .Anal. Calcd for $C_{10}H_{14}N_2O_2S$ (226): C; 53.08, H; 6.24; N; 12.38. Found: C; 52.92, H; 6.32, N; 12.45.

3-imino-3-(2-(2-morpholino-2-oxoethylidene)-4-oxo-thiazolidin-3-yl)pro-panenitrile(2a),3-(2-chloro-1-iminoethyl)-2-(2-morpholino-2-oxoethylidene) thiazolidin -4-one (2b).

To a solution of (**1a)** (0.01mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL) either chloroacetonitrile or malo-nonitrile (0.01mol) was added. The reaction mixture was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from ethanol.

2a: brown crystals, yield 72 %, m.p. 232-34 ºC. IR (KBr, cm^{-1}): 3252(NH), 1716, and 1620 (C=O thiazolidinone and amide). MS m/z (%): 301 (M^+, 0.31) . Anal. Calcd for $C_{11}H_{12}ClN_3O_3S$ (301): C; 43.78, H; 4.01; N; 13.93. Found: C; 43.91, H; 4.22, N; 14.12.

(2 b): grey powder, yield 59 %, m.p. 220-22 ºC. IR (KBr, cm^{-1}): 3210 (NH), 2208(CN), 1710, and 1622 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 3.33(s, 4H, $2CH_2$-mor), 3.77(s, 4H, $2CH_2$-mor) ,3.89 (s, 2H, CH_2CN), 4.01 (s, 2H CH_2-thiazolidinone), 5.43 (s, 1H, NH, exchangeable with D_2O), 5.87(s, 1H, methine-H). MS m/z (%): 292 (M^+= 0.53), Anal. Calcd for $C_{12}H_{12}N_4O_3S$ (292): C; 49.31, H; 4.14; N; 19.17. Found: C; 49.56, H; 3.96, N; 20.10.

5 -amino-6-chloro-7-(2-chlorophenyl)-8-(morpholine-4-carbonyl)-2H-thiazolo [3,2-a]pyridin-3(7H)-one (3)

To a solution of **(1a)** (0.01mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5mL), 2-chlorobenzaldehyde (0.01mol), and chloroacetonitrile (0.01mol) were added. The reaction mixture was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from ethanol.

3: yellow crystals, yield 65 %, m.p. 245-47ºC. IR (KBr, cm^{-1}): 3252, 3078 (NH_2), 1712, and 1620 (C=O thiazolidinone and amide). MS m/z (%): 425 (M^+, 0.11). Anal. Calcd for $C_{18}H_{17}Cl_2N_3O_3S$ (425): C; 50.71, H; 4.02; N; 9.86. Found: C; 50.93, H; 4.11, N; 9.70.

5-arylmethylidine-2-(2-morpholino-2-oxoethylidene) thiazolidin-4-one (4a, b)

To a solution of **(1a)** (0.01mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5mL), either 2-chlorobenzaldehyde (0.01mol), or p-tolualdehyde (0.01mol) was added. The reaction mixture was heated under reflux for 3h. The solid products formed were collected by filtration and recrystallized from ethanol.

.**4a:** yellow crystals, yield 81 %, m.p. 130-32 ºC. IR (KBr, cm^{-1}): 3252 (NH), 1696, and 1628 (C=O thiazolidinone and amide). MS m/z (%): 350 (M^+, 9.74). Anal. Calcd for $C_{16}H_{15}ClN_2O_3S$ (350): C; 54.78, H; 4.31; N; 7.99. Found: C; 54.62, H; 4.11, N; 8.20.

4b: orange powder, yield 62 %, m.p. 120-22 ºC. IR (KBr, cm^{-1}) 3178 (NH), 1698, and1620 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 3.33 (s, 4H, $2CH_2$-mor), 3.77 (s, 4H, $2CH_2$-mor), 5.44 (s, H, NH, exchangeable with D_2O) 6.10 (s, 1H, methine-H), 7.24-7.44 (5H, m,Ar-H and methine-H) . MS m/z (%): 330 (M^+, 100). Anal. Calcd for $C_{17}H_{18}N_2O_3S$ (330): C; 61.80, H; 5.49; N; 8.48 Found: C; 61.62, H; 5.73, N; 8.32.

2-(3-(2-chlorophenyl)-2H-pyrazolo[3,4-d]thiazol-5(6H)-ylidene)-1-morpholin-oethanone (5*)*

To a solution of **(4a)** (0.01mol) in absolute ethanol (20 mL), hydrazine hydrate (0.01mol) was added. The reaction mixture was heated under reflux for 2h. The solid product formed was collected by filtration and recrystallized from ethanol.

5: brown crystals, yield 71 %, m.p. 140-42 ºC. IR (KBr, cm^{-1}): 3178(NH), and 1622 (C=O amide). ^{1}H NMR (DMSO-d_6) δ 3.33 (s, 4H, $2CH_2$-mor), 3.62 (s, 4H,

2CH_2-mor), 7.16-7.62 (5H, m, Ar-H and methine-H) , 8.16 (s, H, NH, exchangeable with D_2O),8.97 (s, H, NH, exchangeable with D_2O). Anal. Calcd for $C_{16}H_{15}ClN_4O_2S$ (362): C; 52.96, H; 4.17; N; 15.44 Found: C; 53.11, H; 4.32, N; 15.52.

5-amino-2-(2-chlorobenzylidene)-7-(2-chlorophenyl)-8-(morpholine-4-carbonyl)-3-oxo-3,7- dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile(6)

To a solution of **(4a)** (0.01mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.05 mL), a mixture of 2-chlorobenzaldehyde (0.01mol) and malononitrile (0.01mol) was added. The reaction mixture was heated under reflux for 2h. The solid product formed was collected by filtration and recrystallized from ethanol.

6: yellow powder, yield 82 %, m.p. 195-97 ºC. IR (KBr, cm^{-1}): 3386, 3292(NH_2), 2194 (C≡ N), 1698, and 1644 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 4H, 2CH_2-mor), 2.49 (s, 4H, 2CH_2-mor), 4.44 (s, 1H, pyridine-H), 5.07 (s, 2H, NH_2, exchangeable with D_2O),7.28-7.69 (9H, m, Ar-H and methine-H) .Anal. Calcd for $C_{26}H_{20}Cl_2N_4O_3S$ (538): C; 57.89, H; 3.74; N; 10.39 Found: C; 58.12, H; 3.95, N; 10.21.

5-amino-2-(3-morpholino-3-oxo-1-p-tolylprop-1-en-2-yl)-7-p-tolyl-7H-pyrano [2,3-d]thiazole-6-carbonitrile (7)

To a solution of **(4b)** (0.01mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.05 mL), a mixture of p-toulaldehyde (0.01mol) and malononitrile (0.01mol) was added. The reaction mixture was heated under reflux for 2h. The solid product formed was collected by filtration recrystallized.

7: red powder, yield 67 %, m.p. 140-42ºC. IR (KBr, cm^{-1}): 3310, 3204 (NH_2), 2202 (C≡ N), and 1632 (C=O amide). ^{1}H NMR (DMSO-d_6) δ 2.29(s, 6H, 2CH_3) 3.35 (s, 4H, 2CH_2-mor), 3.76 (s, 4H, 2CH_2 -mor), 4.91 (s, 1H, pyan-H), 7.21 (s, 2H, NH_2, exchangeable with D_2O),7.28-7.69 (9H, m, Ar-H and methine-H) . MS m/z (%): 498 (M^+, 0.87) . Anal. Calcd for $C_{28}H_{26}N_4O_3S$ (498): C; 67.45, H; 5.26, N; 11.24 Found: C; 68.01, H; 5.30, N; 11.32.

1-(2-(2-chlorobenzylidene)-7-(2-chlorophenyl)-6-cyano-8-(morpholine-4-carbonyl)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-yl)-3-ethylthiourea (8)

To a solution of **(6)** (0.01mol) in DMF (20 mL), sodium hydroxide (0.01mol), and phenylisothiocynate (0.01mol) were added. The reaction mixture was stirred at room temperature for 3h. The solid product formed was collected by filtration and recrystallised from ethanol.

8: yellow crystals, yield 82 %, m.p. 230-32 ºC. IR (KBr, cm^{-1}): 3226, (NH), 2198 (C≡ N), 1702, and 1628 (C=O thiazolidinone, and amide). ^{1}H NMR (DMSO-d_6) δ 3.34 (s, 4H, $2CH_2$-mor), 3.93 (s, 4H, $2CH_2$-mor), 5.10 (s, 1H, pyridine-H), 6.12 (s, 1H, NH, exchangeable with D_2O),7.21-7.87 (9H, m, Ar-H and methine-H), 12.01(br, 1H, SH) . Anal. Calcd for $C_{29}H_{25}Cl_2N_5O_3S_2$ (625): C; 55.59, H; 4.02, N; 11.18 Found: C; 56.20, H; 4.23, N; 11.23.

4,10-dihydro-3,10-(2-chlorophenyl)-8-amino-9-cyano-11(morpholino-4-carbonyl) -pyrazolo[4,5-c]-thiazolo [3,2-a]pyridine(9)

To a solution of (**6)** (0.01mol) in absolute ethanol (20 mL), hydrazine hydrate (0.01) was a dded. The reaction mixture was heated under reflux for 2h. The solid product formed was collected by filtration and recrystallised from ethanol.

9: brown crystals, yield 57 %, m.p. 100-02 ºC. IR (KBr, cm^{-1}): 3294, 3200(NH_2), 3136 (NH), 2200 (C≡ N), and 1620 (C=O amide). ^{1}HNMR (DMSO-d_6) δ 3.33 (s, 4H, $2CH_2$-mor), 3.60 (s, 4H, $2CH_2$-mor), 4.14 (s, 1H, pyridine-H), 6.84-7.74 (10H, m, Ar-H and NH_2, exchangeable with D_2O), 8.91 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{26}H_{20}Cl_2N_6O_2S$ (550): C; 56.63, H; 3.66, N; 15.24 Found: C; 56.92, H; 3.86, N; 15.40.

2,3,10-triihydro-2-(o-chlorophenylmethylidine)-3,9-dioxo-9-(2-chlorophenyl)-11 (morpholino-4-carbonyl)- thiazolo[3,2-a]-3-aza-1,8- naphthyridine(10)

To a solution of **(6)** (0.01mol) enough quantity of formic acid was added. The reaction mixture was heated under reflux for 6h. The solid product formed was collected by filtration recrystallised from ethanol.

10: brown crystals, yield 57 %, m.p. 230-32 ºC. IR (KBr, cm^{-1}): 3210 (NH), 1712, and 1622 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 3.29 (s, 4H, $2CH_2$-mor), 3.58 (s, 4H, $2CH_2$-mor), 4.00(s, 1H, pyridine-H),6.13 (s, 1H, pyrimidine-H), 7.43-7.71 (9H, m, Ar-H and methine-H), 12.00 (s, 1H, NH, exchangeeable with D_2O). Anal. Calcd for $C_{27}H_{20}Cl_2N_4O_4S$ (566): C; 57.15, H; 3.55, N; 9.87 Found: C; 57.32, H; 3.76, N; 9.75.

2,3,10-triihydro-2-(o-chlorophenylmethylidine)-3,9-dioxo-7-phenyl-9-(2-chloro-phenyl)-8-imino- 11(morpholine-4-carbonyl)- thiazolo[3,2-a]-3-aza-1,8-naphtha-yridine(11)

To a solution of **(6)** (0.01mol) in benzene (20 mL), benzoyl chloride (0.01 mol) was added .The reaction mixture was heated under reflux for 6h. The solid product formed was collected by filtration and recrystallised from ethanol.

11: yellow crystals, yield 51 %, m.p. 163-65 ºC. IR (KBr, cm^{-1}): 3132 (NH), 1712, and 1622 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO-d_6) δ 3.34 (s, 4H, $2CH_2$-mor), 3.58 (s, 4H, $2CH_2$-mor), 5.12(s, 1H, pyridine-H), 7.43-7.72 (14 H, m, Ar-H and methine-H) 12.12 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{33}H_{24}Cl_2N_4O_4S$ (642): C; 61.59, H; 3.76, N; 8.71 Found: C; 61.72, H; 3.92, N; 8.95.

2,3,10-triihydro-2-(o-chlorophenylmethylidine)-3-oxo-7-thiohydroxy-8-imino-9-thione-10-(2-chlorophenyl)- 11(morpholino-4-carbonyl)- thia-zolo[3,2-a]-3-aza-1,8- naphthyridine (12)

To a solution of **(6)** (0.01mol) in pyridine (20 mL), carbon disulphide (0.01 mol) was added .The reaction mixture was heated under reflux for 6h. The solid product formed was collected by filtration and recrystallized from ethanol.

12: brown powder, yield 49 %, m.p. 250-52 ºC. IR (KBr, cm^{-1}): 3504 (SH), 3154 (NH), 1720, and 1616 (C=O thiazolidinone and amide). ^{1}H NMR (DMSO -d_6) δ 3.31 (s, 4H, $2CH_2$-mor), 3.58 (s, 4H, $2CH_2$-mor), 5.01(s, 1H, pyridine-H), 6.13 (s, 1H, NH, exchangeable with D_2O), 7.45-7.70 (9 H, m, Ar-H and methine-H), 12.01(br, 1H, SH) . Anal. Calcd for $C_{27}H_{20}Cl_2N_4O_3S_3$ (614): C; 52.68, H; 3.27, N; 9.10 Found: C; 52.81, H; 3.42, N; 8.89.

2,3,10-triihydro-2-(o-chlorophenylmethylidine)-3-oxo-7,9-diaminoi-8-cyano--10-(2-chlorophenyl) -11(morpholino-4-carbonyl)- thiazolo[3,2-a]- 1,8-naphthyrid-ine(13)

To a solution of **(6)** (0.01mol) in ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL), malononitrile (0.01 mol) was added .The reaction mixture was heated under reflux for 6h. The solid product formed was collected by filtration recrystallized from ethanol.

13: yellow powder, yield 82 %, m.p. > 360ºC. IR (KBr, cm^{-1}): 3432, 3312(NH_2), 2212(CN), 1719, and 1621 (C=O thiazolidinone and amide) . ^{1}H NMR (DMSO-d_6) δ 3.33 (s, 4H, $2CH_2$-mor), 3.59 (s, 4H, $2CH_2$-mor), 5.10 (s, 1H, pyridine-H), 7.68-7.88 (13 H, m, Ar-H, methine-H and 2 NH_2, exchangeable with D_2O). MS m/z (%) : 604

(M^+, 0.24) .Anal. Calcd for $C_{29}H_{22}Cl_2N_6O_3S$ (604): C; 57.52, H; 3.66, N; 13.88 Found: C; 57.62, H; 3.45, N; 13.54.

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