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Novel One-pot Synthesis of Thiazolo[3,2-*a*] Pyrimidin-5-one as a Key Compound for Poly Nuclear Heterocycles

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3-AMINO-2- hydroxy-7-methyl- thiazolo[3,2-*a*]pyrimidin-5-one (5) was synthesized by one-pot reaction from 2-bromo cyanoacetamide, ethyl acetoacetate and thiourea. The new 3-amino-2-hydrazino derivatives (15,18), 2-pyrazol- thiazolo [3,2-*a*] pyrimidin -5-ones (14,17,20) and 2-(4-arylidene) -pyrazol-thiazolo [3,2-*a*] pyrimidin-5-ones (22a-d) were synthesized through facile condensing procedures starting from 3-amino-2-hydrazino-7-methyl-thiazolo[3,2-*a*]pyrimidin-5-one (12). The newly synthesized products were characterized by their IR, ESI-MS, NMR and micro analytical data.

Keywords: Thiazolo [3,2-*a*] pyrimidin-5-one, One pot synthesis, Condensation, Intramolecular Cyclization and Tautomerism.

Thiazolopyrimidines are bicyclic heterocycles, formed by the reaction of 1,2-dielectrophiles with a pyrimidin-2(1*H*)-thione skeleton[1-4]. They receive diverse pharmacological applications such as anti-HIV [5,6], antibacterial[7,8], anticancer [9], anti-inflammatory[10-12], antimalarial[5], antimicrobial[12,13], anti-HSV-1[14] and herbicidal [15] activities. Furthermore, some thiazolopyrimidines have been assigned as new acetylcholin esterase inhibitors, especially for the treatment of Alzheimer's disease[16]. The aim of our study is to synthesis 3-amino-2-hydroxy-7- methyl-thiazolo[3,2-*a*]pyrimidin-5-one (5) to use it for the preparation of the 3-amino-2-hydrazino derivative (12).

Discussion

Compound 5 is produced *via* one-pot synthesis of 2-bromocyanoacetamide, ethyl acetoacetate and thiourea in ethoxide solution *via* the intermediate 3-amino-3-hydroxy-2-(4-methyl-6-oxo-1,6-dihydro-pyrimidin-2-ylsulfanyl)-acrylo nitrile (2) (Scheme 1, *Path A*). *Path B* is considered to be a possible alternative to produce the final product 11 through the intermediate 8. We have reasons to believe that the reaction mechanism obeyes *path A* to form the intermediate 2, which undergoes intramolecular cyclization at N3 to produce the cyclized intermediate 3. In the presence of strong basic medium, the latter intermediate undergoes hydrolysis followed by elimination of amido group to furnish the final fused pyrimidine system **(***cf.* 5).

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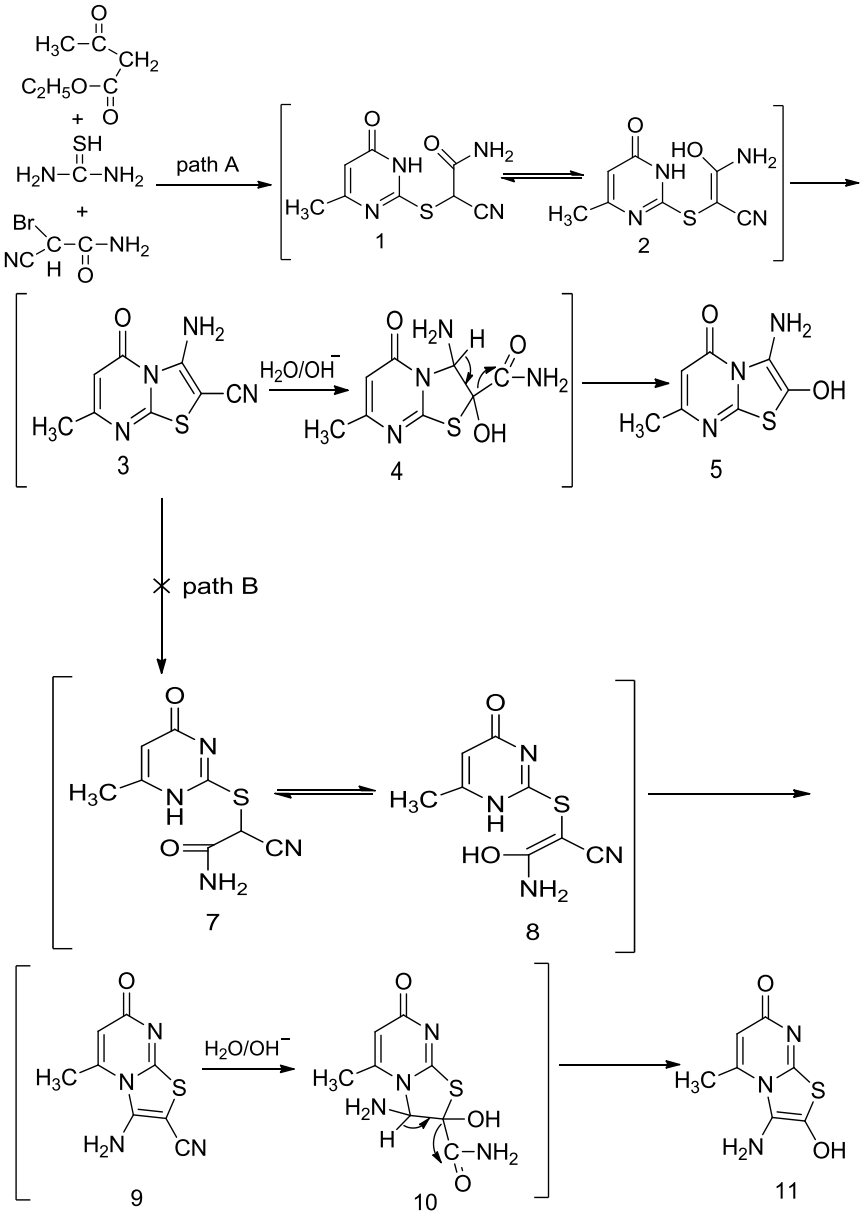
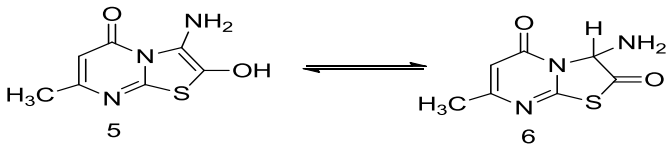


Scheme 1. Mechanistic pathway leading to the synthesis of 3-amino-2-hydroxy-7-methyl-thiazolo[3,2-*a*] pyrimidin-5-one (5) and not to 3-amino-2-hydroxy-5-methyl-8,8a-dihydro-thiazolo[3,2-*a*]pyrimidin-7-one (11) .

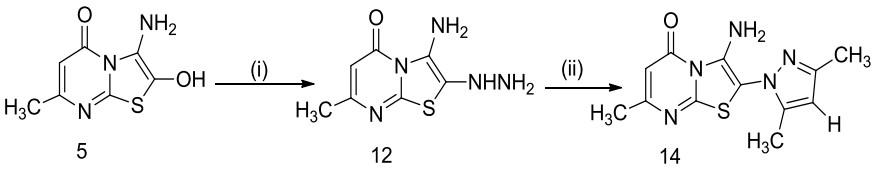
Our assumption is based upon two facts; firstly, our previous experience in the synthesis of fused pyrimidines including thiazolopyrimidines[17] and thienopyrimidines[18,19]. Secondly, literature survey which disclosed that N3 is the prime position for hetero cyclization in acidic or basic media[20-21]. The presence of an equilibrium between the two tautomeric structures of keto and enol forms (Scheme 2) is based on the spectral analyses. The ^{1}H-NMR spectrum revealed a singlet signal integrated for one proton at 03.20 ppm attributed to methine proton of the thiazolone ring of the keto form 6. The spectrum also exhibited one D_2O exchangeable singlet signal integrated for one proton at δ 10.8 ppm attributed to OH group of the enol form 5. The IR spectrum displayed bands at 3766 cm^{-1} corresponding to broad OH group of the enol form 5 and at 1716 cm^{-1} corresponding to (C=O) of the thiazolone ring of the keto form 6. The electron impact mass spectrum of compound 5 showed a peak at *m/z* 198 (5%) corresponding to (M^+ +1).



Scheme 2. The keto-enol type of tautomerism.

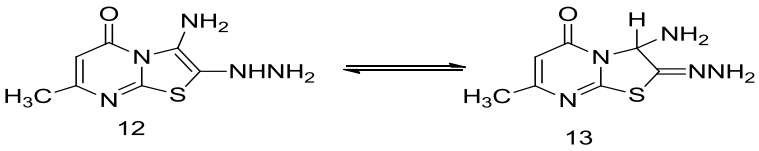
The strategies adopted for the synthesis of the new compounds are depicted in Schemes (3-10).

Scheme 3 comprises the direct hydrazinolysis of compound 5 with hydrazine hydrate to give the corresponding 3-amino-2-hydrazino-7-methyl-thiazolo[3,2-*a*] pyrimidin-5-one (12). Structure of compound 12 is confirmed on the basis of elemental analyses and spectral data. The electron impact mass spectrum of compound 12 showed a peak at *m/z* 212 (7%) corresponding to (M^+ +1). The ^{1}H-NMR spectrum exhibited one D_2O exchangeable singlet signal integrated for two protons at δ 04.45 ppm attributed to broad NH_2 group of the thiazolone ring and a D_2O exchangeable broad signal integrated for three protons at δ 08.7 ppm attributed to NH+NH_2 groups. The IR spectrum revealed the absence of OH group and displayed bands at 3105cm^{-1} corresponding to broad NH group and bands at 3426, 3337 cm^{-1} corresponding to broad $2NH_2$ groups.



Scheme 3. **Synthetic pathways for compounds 12 and 14. Reagents & conditions: i: Hydrazine hydrate 99%/ acetic acid (1ml) / abs. ethanol/reflux; ii: Pentan-2,4-dione/ dry dioxane/ reflux.**

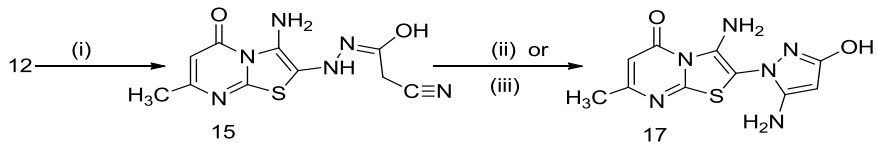
Scheme 4 shows the tautomerism in compound 12 which is based on the spectral data. The ^{1}H-NMR spectrum of compound 13 revealed a singlet signal integrated for one proton at δ 02.07 ppm attributed to methine proton of the thiazol ring.



Scheme 4. The tautomerism of the two forms 12 and 13.

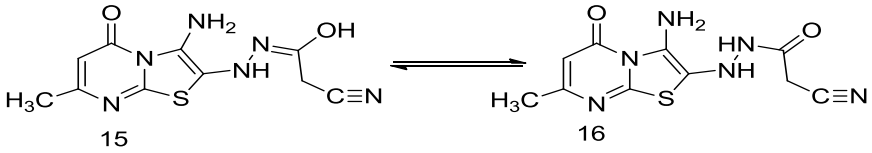
3-Amino-2-(3,5-dimethyl-pyrazol-1-yl)-7-methyl-thiazolo[3,2-*a*]pyrimidin-5-one (14) (Scheme 3) was obtained in good yield by condensing compound 12 with an equimolecular amount of pentan-2,4-dione. Structure of compound 14 was confirmed on the basis of elemental analyses and spectral data. The ^{1}H-NMR spectrum of 14 revealed two singlet signals each integrated for three protons at δ 02.15, 02.19 ppm attributed to the two CH_3 groups of the pyrazole ring. In addition, a singlet signal integrated for one proton appeared at 06.14 ppm and attributed to the methine proton of the pyrazole ring. The ^{13}C-NMR spectrum of compound 14 showed peaks at δ 13.8, 14.8 ppm assigned for $2CH_3$ groups of the pyrazole ring and at 110.9 ppm assigned for (CH) of the pyrazole ring. Also, the IR spectrum of compound 14 displayed a band at 1670 cm^{-1} corresponding to (C=O) group of the pyrimidone ring and a broad band at 3385 cm^{-1}, 3288 cm^{-1} corresponding to the NH_2 group. The electron impact mass spectrum of compound 14 showed a peak at m/z 276 (100%) corresponding to (M^+ +1).

Compound 12 is further utilized for the synthesis of N'-(3-amino-7-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-2-yl)-2-cyano aceto hydrazide (15) and 3-amino-2- (5-amino-3- hydroxy-1*H*-pyrazolyl) -7-methyl-5*H*-thiazolo [3,2-*a*]pyrimidin-5-one (17), respectively (Scheme 5). This is accomplished through the reaction of compound 12 with ethyl cyanocetate in absolute ethanol with subsequent elimination of ethanol molecule to afford compound 15. Structure of compound 15 is confirmed on the basis of elemental analyses and spectral data. The electron impact mass spectrum of compound 15 showed a peak at *m/z* 279 (5%) corresponding to (M^+ +1). The IR spectrum of compound 15 displayed a band at 2215 cm^{-1} corresponding to the (CN) group.



Scheme 5. Synthetic pathways for compounds 15 and 17. Reagents & conditions: i: Ethyl cyanoacetate/abs. ethanol/reflux (2h); ii: Abs. ethanol/reflux (12h); iii: Sod. ethoxide/abs.ethanol/ reflux (6h).

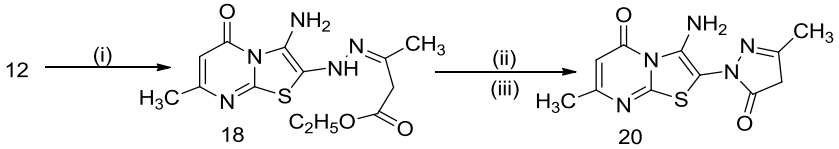
The presence of the keto-enol form of compounds 15 and 16 (Scheme 6) is elucidated with the help of spectral data. Thus, the ^{1}H-NMR spectrum revealed a D_2O exchangeable singlet integrated for one proton at 03.98 ppm which is attributed to alcoholic OH group, indicating the presence of the enol form 15. The IR spectrum displayed bands at 3757 cm^{-1} corresponding to broad OH group, which indicates the presence of the enol form 15 and at 1630 cm^{-1} corresponding to (C=O) group, which indicates the presence of the keto form 16.



Scheme 6. The tautomerism in the two forms 15 and 16.

Cyclizing compound 15 *either* by prolonged heating in absolute ethanol *or* by heating in ethanolic sodium ethoxide solution, produced compound 17. Its ^{1}H-NMR spectrum revealed a singlet signal integrated for one proton at 06.3 ppm attributed to the methine proton of the pyrazole ring. The electron impact mass spectrum of compound 17 showed a peak at *m/z* 279 (45%) corresponding to (M^+ +1).

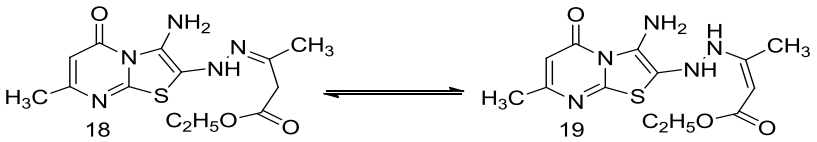
Structure of compound 18 (Scheme 7) was elucidated with the help of spectral data. The ^{1}H-NMR spectrum of the compound 18 revealed the presence of one triplet and one quartet signals at δ 01.14 and 04.02 ppm attributed to CH_3CH_2 of ethyl ester group. This means that the condensation reaction of compound 12 with ethyl acetoacetate in absolute ethanol eliminated a water molecule not an ethanol molecule. The IR spectrum displayed a band at 1740 cm^{-1} corresponding to (C=O) of the ethyl ester group and also its electron impact mass spectrum showed a peak at *m/z* 324 (4.16%) corresponding to (M^+ +1).



Scheme 7. Synthetic pathways for compounds 18 and 20. Reagents & conditions: i: Ethyl acetoacetate/ abs. ethanol/reflux (2h); ii: Sod. ethoxide/abs.ethanol/ reflux (2h); iii:Abs. ethanol/ reflux (6h).

The tautomerism in compounds 18 and 19 (Scheme 8) was confirmed from the ^{1}H-NMR spectrum which revealed the presence of a singlet signal integrated for two protons at δ 01.9 ppm attributed to active methylene in chain, which indicates the presence of the form 18. In addition, a singlet signal integrated for one proton appeared at δ 05.9 ppm due to methine proton in the chain, which

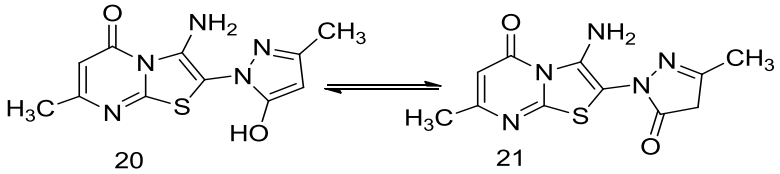
indicates the presence of the form 19. The ^{13}C-NMR spectrum showed signals at δ 42.3 ppm corresponding to the active methylene of the form 18, at δ 90.9 ppm corresponding to methine carbon atom of the form 19, at 162.7 ppm due to (C=O) group of the pyrimidone ring and at 169.4 ppm 170.5 ppm corresponding to two (C=O) groups of the ethyl ester group in the two forms 18 and 19.



Scheme 8. The tautomerism in the two forms 18 and 19.

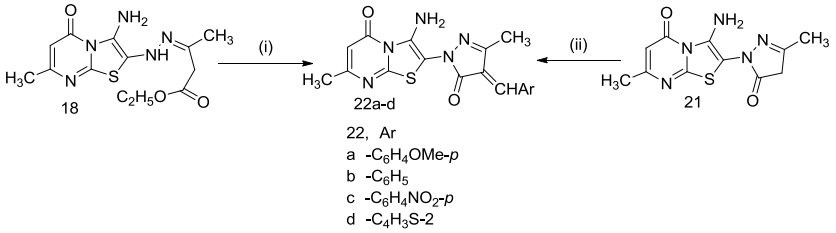
3-Amino-7-methyl-2-(3-methyl-5-oxo-4,5-dihydro-pyrazolyl) -thiazolo[3,2-*a*] pyrimidin-5-one (20) (Scheme 7) could be produced by cyclization of compound 18 *either* by heating in absolute ethanol *or* by heating in ethanolic sodium ethoxide solution. Its ^{1}H-NMR spectrum revealed the presence of a singlet signal integrated for three protons at δ 1.8 ppm attributed to CH_3 group in the pyrazolone ring, while its electron impact mass spectrum showed a base peak at *m/z* 278 corresponding to (M^+ +1).

The keto-enol type of tautomerism in compound 20 (Scheme 9) is outlined from the ^{1}H-NMR spectrum which revealed the presence of a singlet signal integrated for two protons at δ 02.5 ppm attributed to active methylene in the pyrazolone ring of the form 21 and a singlet signal integrated for one proton at δ 05.9 ppm attributed to methine proton in the pyrazole ring of the form 20. The ^{13}C-NMR spectrum showed signals at δ 42.3 ppm corresponding to (CH_2) and at 162,166 ppm corresponding to (2C=O) groups of the pyrimidone ring and of the form 21. In addition, a signal appeared at δ 90 ppm corresponding to (CH) of the pyrimidone ring and at δ 91.5 ppm corresponding to (CH) of the pyrazole ring of the form 20. The IR spectrum displayed bands at 3700cm^{-1} corresponding to (OH) of the pyrazole ring of the form 20 and at 1637 cm^{-1}, 1680 cm^{-1} corresponding to (2C=O) groups of the pyrimidone ring and of the pyrazolone ring of the form 21.



Scheme 9. The tautomerism in compounds 20 and 21.

The synthesis of the Schiff's bases 22(a-d) could be produced by condensing compound 18 with aromatic and heterocyclic aromatic aldehydes, upon heating under reflux in dry pyridine \ piperidine mixture (1:1) or by condensing compound 21 with aromatic and heterocyclic aldehydes under fusion at 140^{o}C (Scheme 10).



Scheme 10. Synthetic pathways for compounds 22a-d. Reagents & conditions: i:The appropriate aromatic or heterocyclic aldehydes /dry pyridine /reflux; ii: The appropriate aromatic or heterocyclic aldehydes / fusion at 140°C.

Structure of compound 22a (Scheme 10) was confirmed on the basis of elemental analyses and spectral data. Its electron impact mass spectrum showed a peak at *m/z* 396 (5%) corresponding to (M^+ +1). The ^{1}H-NMR spectrum of compound 22a revealed the absence of the signal attributed to active methylene and the presence of a singlet signal integrated for three protons at δ 03.7 ppm which is attributed to the CH_3O group and a singlet signal integrated for one proton at δ 08.8 ppm for the azomethine proton. The IR spectrum of compound 22a exhibited absorption bands at 1719 cm^{-1} due to (C=O) group of the pyrazolone ring, 1665 cm^{-1} due to (C=O) group of the pyrimidone ring and at 3429, 3370 cm^{-1} due to the NH_2 group.

Experimental

Chemistry

All melting points are uncorrected and determined on Gallenkamp electric melting point apparatus. The IR spectra were recorded (KBr) on a Perkin-Elmer 1430 spectrometer (National Research Centre). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in δ ppm scale on Jeol ECA 500 spectrometer, run at 500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR (National Research Centre) with TMS ($SiMe_4$) as internal standard. The coupling constant values are reported in Hz. Mass spectra were recorded on GCMS-QP 1000 EX Shimadzu Japan (Gas Chromatography-Mass spectrometer). Elemental analytical data (in accord with the calculated values) were obtained at the Elemental Analytical Centre at National Research Centre, Egypt. All reactions were followed and the purity of the newly synthesized compounds were assessed by thin layer chromatography (TLC) Merck Alufolien Kieselgel Silica Gel 60 F254 (aluminum sheets 20×20 cm) using $CHCl_3/CH_3OH$ (9:1 v/v) as eluent and detected by UV-absorpion at 254 nm.

Synthesis of 3-amino-2-hydroxy-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (5)

A mixture of 2-bromo cyanoacetamide (10 mmole), ethyl acetoacetate (10 mmole) and thiourea (10 mmole) in ethoxide solution prepared by dissolving sodium metal (0.79gm, 30 mmole) in 30 ml of absolute ethanol (dry conditions) was heated under reflux for 5h. The precipitate separated by pouring the reaction mixture onto 10 ml of ice-water was collected and washed with 10 ml ethanol

and dried then crystallized from DMF:H_2O (1:1). White powder, yield, 85%, m.p. 228-230˚C. IR (KBr) cm^{-1}: 3766 cm^{-1} (OH); 3385, 3288 cm^{-1} (NH_2); 1716, 1675 cm^{-1} (2C=O) groups. ^{1}H-NMR (DMSO-d_6, 500MHz) δ (ppm): 01.9 ppm (s, 3H, CH_3); 03.2 ppm (s, 1H, CH of the new thiazole ring); 05.3 ppm (s, 1H, CH of pyrimidine ring); 07.3 ppm (br.s, 2H, NH_2, D_2O exchangeable); 10.8 ppm (br.s, 1H, OH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ (ppm): δ 18.6(CH_3), 42(CH), 99.2(C_2), 104.1(C_5), 151.9(C_3), 153.6(C_6), 153.7(C_8), 164.7(tertary amidic (C=O) group in the pyrimidone ring), 171((C=O) group in thiazolone ring). MS. (m/z, %):198 (M^+ +1, 100); 166(83); 96(55). Anal. Calcd for $C_7H_7N_3O_2S$ (197): C, 42.63; H, 03.58; N, 21.31; S,16.26 (%). Found: C, 42.73; H, 03.59; N, 21.33; S,16.25 (%).

Synthesis of 3-amino-2-hydrazinyl-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (12)

A mixture of compound 5 (01.97 gm, 10 mmole) and hydrazine hydrate 99% (6ml) in catalytic amount of acetic acid (1ml) were refluxed in ethanol (30 ml) for 5 h. The reaction mixture was allowed to cool to room temperature. The solid was collected by filtration then crystallized from 60% ethanol.

Yellow powder, yield, 40%, m.p. 290-292˚C. IR (KBr) cm^{-1}: 3426-3237 cm^{-1} ($2NH_2$); 3109 cm^{-1} (NH); 2924 cm^{-1} (CH-aliphatic); 1675 cm^{-1} (C=O). ^{1}H-NMR (DMSO-d_6, 500MHz) δ (ppm): 01.9 ppm (s, 3H, CH_3), 02.0 ppm (s, 1H, CH of the thiazole ring), 04.45 ppm (br.s, 2H, NH_2, disappeared by D_2O exchange), 05.3 ppm (s, 1H, CH of the pyrimidone ring), 08.7 ppm (br. s, 3H, (NH+ NH_2), disappeared by D_2O exchange). MS. (m/z, %): 212 (M^++1, 5); 166(100); 96(65). Anal. Calcd for $C_7H_9N_5OS$ (211): C, 39.80; H, 04.29; N, 33.15; S, 15.18 (%). Found: C, 39.71; H, 04.30; N, 33.17; S, 15.19 (%).

Synthesis of 3-amino-2-(3,5-dimethyl-1H-pyrazolyl)-7-methyl-5H-thiazolo[3,2-a] pyrimidin-5-one (14)

A mixture of compound 12 (02.11gm,10 mmole) and pentan-2,4-dione (10 mmole) was heated under reflux in dry dioxane (30 ml) for 5 h. The reaction mixture was allowed to cool to room temperature and the solid precipitate was filtered off, washed thoroughly with ethanol and dried then crystallized from dioxane.

Yellow powder, yield, 55%, m.p. 132-134˚C. IR (KBr) cm^{-1}: 3440 cm^{-1}, 32700 cm^{-1} NH_2 group and 1670 cm^{-1} (C=O) group. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 02.15 ppm (s, 3H, CH_3 of the pyrimidine ring); 02.19 ppm (s, 3H, CH_3 of pyrazole ring); 02.50 ppm (s, 3H, CH_3 of the new pyrazole ring); 05.33 ppm (s, 1H, CH of pyrimidine ring); 06.14 ppm (s, 1H, CH of the new pyrazole ring); 12.12 ppm (br.s, 2H, NH_2, disappeared by D_2O exchange).^{13}C-NMR (DMSO-d_6, 125 MHz) δ (ppm): δ 13.8 ppm and 14.8 ppm (two carbon atoms of $2CH_3$ groups of the new pyrazole ring), 23.8(CH_3 group of the pyrimidone ring), 107.4(CH of the pyrimidone ring), 110.9 (CH of the new pyrazole ring) and at 164.7 ((C=O) group in the pyrimidone ring). MS. (m/z, %): 276 (M^+ +1, 100); 166 (80); 96(60). Anal. Calcd for $C_{12}H_{13}N_5OS$ (275): C, 52.35; H, 4.76; N, 25.44; S, 11.65 (%). Found: C, 52.25; H, 04.75; N, 25.43; S, 11.66 (%).

Synthesis of N'-(3-amino-7-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-2-yl)-2-cyanoacetohydrazide (15)

A mixture of compound 12 (02.11gm, 10 mmole) and ethyl cyanoacetate (01.33gm, 10 mmole) was heated under reflux in absolute ethanol (30 ml) for 2 h. The reaction mixture was allowed to cool to room temperature and the solid precipitate was filtered off, washed thoroughly with ethanol and dried then crystallized from dioxane.

Yellow powder, yield, 55%, m.p. 243-245˚C. IR (KBr) cm^{-1}: 3750 cm^{-1} (OH); 3432, 3337 cm^{-1} (NH_2); 3237, 3154 cm^{-1} (2NH); 2923 cm^{-1} (CH-aliphatic); 2215 cm^{-1} (CN); 1640, 1630 cm^{-1} (2C=O).^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 01.9 ppm (s, 3H,CH_3); 03.1 ppm (s, 2H,CH_2); 04.5 ppm (br. s, 1H, ethanolic (OH), disappeared by D_2O exchange); 05.3 ppm (s, 1H, CH of the pyrimidone ring); 08.7 ppm (br.s, 2H, NH_2, disappeared by D_2O exchange); 09.8 ppm (br.s, 2H, 2NH, disappeared by D_2O exchange). MS. (m/z, %): 279 (M^+ +1, 5); 140 (50); 69 (100). Anal. Calcd for $C_{10}H_{10}N_6O_2S$ (278): C, 43.16; H, 03.62; N, 30.20; S, 11.52 (%). Found**:** C, 43.07; H, 03.61; N, 30.29; S, 11.51 (%).

Synthesis of 3-amino-2-(5-amino-3-hydroxy-1H-pyrazolyl)-7-methyl-5H-thiazolo [3,2-a] pyrimidin-5-one (17)

Method (A)

A solution of compound 15 (02.78gm, 10mmole) in 30 ml absolute ethanol, (dry conditions), was heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature, then poured onto ice-water (30 ml). The precipitated solid was filtered off and dried then crystallized from dioxane to produce the pure compound 17 in 65% yield, m.p. (268-270^{o}C).

Method (B)

A solution of compound 15 (02.78gm, 10mmole) in sodium ethoxide solution (prepared by dissolving sodium metal (0.23gm, 10mmol) in 30ml of absolute ethanol), (dry conditions), was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature, poured onto ice-water (30ml), then neutralized with conc. HCl (1ml) , whereby a solid was precipitated, filtered off and dried to produce a compound identical in all aspects with 17 (m.p., mixed m.p. and comparative IR spectra) in 50% yield.

Method (C)

A mixture of compound 12 (02.11gm, 10 mmole) and ethyl cyanoacetate (01.33gm, 10 mmole) was heated under reflux in absolute ethanol (30 ml), (dry conditions), for 12 h. The reaction mixture was poured onto ice-water (10 ml). The solid precipitate was filtered off, washed thoroughly with ethanol and dried to produce compound 17 in 60% yield. The obtained compound has the same data as that obtained from methods (A) and (B).

Red powder, m.p. 268-270˚C. IR (KBr) cm^{-1}: 3500 cm^{-1} (OH); 3409, 3331, 3217, 3170 cm^{-1} ($2NH_2$) and 1693 cm^{-1} (C=O).^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 2.2 ppm (s, 3H, CH_3 of pyrimidine ring); 4.2 ppm (br.s, 2H, NH_2 of

new pyrazole ring, disappeared by D_2O exchange); 5.6 ppm (s, 1H, CH of the pyrimidine ring); 6.3 ppm (s, 1H, CH of the new pyrazole ring); 8.3 ppm (br.s, 2H, NH_2 of the new thiazole ring, disappeared by D_2O exchange); 11.31 ppm (br.s, 1H, OH, disappeared by D_2O exchange). MS**.** (m/z, %): 279 (M^+ +1, 45); 182 (5); 164 (25); 56 (100). Anal. Calcd for $C_{10}H_{10}N_6O_2S$ (278): C, 43.16; H, 03.62; N, 30.20; S, 11.52 (%). Found**:** C, 43.20; H, 03.63; N, 30.25; S, 11.51 (%).

Synthesis of ethyl 3-(2-(3-amino-7-methyl-5-oxo-5H-thiazolo[3,2-a] pyrimidin-2-yl) hydrazono)butanoate (18)

A mixture of compound 12 (02.11gm, 10 mmole) and ethyl acetoacetate (01.30gm, 10mmole) was heated under reflux in absolute ethanol (30 ml) for 2 h. The reaction mixture was allowed to cool to room temperature and the solid precipitate was filtered off, washed thoroughly with ethanol, dried and crystallized from ethanol to produce the pure compound 18.

Yello powder, yield,87%, m.p. 134-136˚C. IR (KBr) cm^{-1}: 3442, 3335 cm^{-1} (NH_2); 3161, 3105 cm^{-1} (2NH); 2923 cm^{-1} (CH-aliphatic); 1739, 1663 cm^{-1} (2C=O).^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 01.14 ppm (t, 3H, *J*=8 Hz, CH_3 of ester group); 01.91, 01.96 ppm (s, 6H, $2CH_3$); 02.0, 2.1ppm (s, 6H, $2CH_3$ of pyrimidone ring); 04.02 ppm (q, 2H, *J*=8 Hz, CH_2 of ester group); 04.2 ppm (br.s, 4H, $2NH_2$, disappeared by D_2O exchange) 05.2,05.3 ppm (s., 2H, 2CH in pyrimidone ring); 05.9 ppm (s., 1H, CH of the form 19); 10.07 ppm (br. s., 2H, (2NH), disappeared by D_2O exchange). ^{13}C-NMR (DMSO-d_6, 125 MHz): δ (ppm): 13.1, 14.5 ($2CH_3$ of ethyl groups); 17.1, 21.8 ($2CH_3$ groups); 23.4, 23.6 ($2CH_3$ groups in the pyrimidone ring); 42.3(CH_2 of the form 18); 60.9(CH_2 of ethyl group); 90.8((CH) of the form 19); 107.9 ((CH) in the pyrimidone ring); 151.2(C_3); 152.5(C_6); 153.9(C_8); 162.7 ((C=O) group in the pyrimidone ring); 169.3, 170.4(2(C=O) of ester group in the forms 18 and 19). MS. (m/z, %): 324(M^+ +1, 4.16); 253(85); 166 (100). Anal. Calcd for $C_{13}H_{17}N_5O_3S$ (323): C, 48.28; H, 05.30; N, 21.66; S, 09.92 (%). Found: C, 48.38; H, 05.29; N, 21.71; S, 09.93 (%).

Synthesis of 3-amino-7- methyl-2- (3-methyl-5-oxo-4,5- dihydro-1H-pyrazolyl) - 5H-thiazolo [3,2-a] pyrimidin-5-one (20)

Method (A)

A solution of compound 18 (03.23gm, 10 mmole) in 30 ml of absolute ethanol (dry conditions), was heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature, poured onto ice-water (10 ml), whereby a solid was precipitated, which was filtered off and crystallized from ethanol to produce the pure compound 20 in 75% yield, m.p. (268-270^{o}C).

Method (B)

A solution of compound 18 (03.23gm, 10 mmole) in sodium ethoxide solution (prepared by dissolving sodium metal (00.23gm, 10 mmol) in 30 ml of absolute ethanol) (dry conditions), was heated under reflux for 2 h till the starting material disappeared (TLC). The reaction mixture was allowed to cool to room temperature, poured onto ice-water (30 ml), and neutralized with conc HCl(1ml),

whereby a solid was precipitated, filtered off and dried to produce compound **20** in 68% yield.

Method (C)

A mixture of compound 12 (02.11gm, 10 mmole) and ethyl acetoacetate (01.30gm, 10 mmole) was heated under reflux in absolute ethanol (30 ml) (dry conditions) for 10 h till the starting material disappeared (TLC). The reaction mixture was allowed to cool to room temperature then poured onto ice-water (10 ml) . The solid precipitate was filtered off, washed thoroughly with ethanol and dried to produce compound 20 in 78% yield. This compound has the same data as that obtained from methods (A) and (B). Orange powder, m.p. 268°-270°C. IR (KBr) cm^{-1}: 3700 cm^{-1} (OH); 3428, 3350 cm^{-1} (NH_2); 3100 cm^{-1} (CH-aromatic); 2924 cm^{-1} (CH-aliphatic); 1680 cm^{-1}, 1637 cm^{-1} (2C=O).^{1}H-NMR (DMSO-d_6, 500MHz) δ (ppm): 01.8 ppm (s, 3H, CH_3 of the pyrazolone ring); 02.18 ppm (s, 3H, CH_3 of pyrimidone ring); 02.5 ppm (s, 1H, CH_2 in the newly pyrazole ring of the form 21); 5.3 ppm (s, 1H, CH of pyrimidone ring); 5.9 ppm (s, 1H, CH of the pyrazole ring of the form 20); 12.5 ppm (br. s, 3H, (NH_2 + OH) disappeared by D_2O exchange). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ (ppm): 12.8(CH_3 group in the pyrazole ring); 23.5(CH_3 group in pyrimidone ring); 42.3(CH_2 of the pyrazolone ring of the form 21); 90 (CH of pyrimidone ring); 91.4 (CH) of the pyrazole ring of the form 20; 98.6 (C_5 of the pyrazole ring in the form 20); 107.9 (C_5); 147.7 (C_2); 148.1 (C_3); 153.9(C_6); 158.92(C_8); 162.1((C=O)group in the pyrimidone ring); 166.1((C=O)group in the newly pyrazolone ring). MS. (m/z, %): 278 (M^+ +1, 100); 166 (25); 96 (11). Anal. Calcd for $C_{11}H_{11}N_5O_2S$ (277): C, 47.64; H, 04.00; N, 25.26; S, 11.56 (%). Found: C, 47.54; H, 04.01; N, 25.21; S, 11.58 (%).

Preparation of compounds 22(a-d)

General procedure (a)

A mixture of compound 18 (03.23gm, 10 mmole) and 10 mmole of the appropriate aromatic or heterocyclic aldehyde in 15 ml of dry pyridine\piperidine mixture (1:1) was heated under reflux for 5 h. The reaction mixture was allowed to cool to room temperature, poured onto water (10 ml) neutralized with (1ml) of HCl (36%), whereby a solid was precipitated, filtered off and crystallized from the proper solvent, to produce the pure derivatives 22(a-d).

General Procedure (B)

A mixture of compound 21 (02.77gm, 10 mmole) and 10 mmole of the appropriate aromatic or heterocyclic aldehyde was heated for 3h at 140°C. The deposited precipitate was crystallized from the proper solvent to produce the pure free derivatives 22(a-d) .

3-Amino-2- (4-(4-methoxybenzylidene) -3-methyl-5-oxo-4,5- dihydro-1H-pyrazolyl)-7-methyl-5H- thiazolo [3,2 a] pyrimidin-5-one (22a)

Dark orange powder, crystallized from ethanol, yield 75%, m.p. 228-230˚C; IR (KBr) cm^{-1}: 3429, 3370 cm^{-1} (NH_2)); 3011 cm^{-1} (CH-aromatic); 2929 cm^{-1}

CH-aliphatic) and 1716, 1662 cm^{-1} (2C=O). ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 01.89 ppm (s, 3H, CH_3 of pyrazolone ring); 01.97 ppm (s, 3H, CH_3 of pyrimidone ring); 03.78 ppm (s, 3H, CH_3O); 05.27 ppm (s, 1H, =CH of pyrimidone ring); 07.01 ppm (d, 2 H, *J* = 9 Hz, Aromatic protons); 07.76 ppm (d, 2 H, *J* = 9 Hz, Aromatic protons); 08.60 ppm ((s, 1H, benzylic proton); 10.79 ppm (br. s, 2H, NH_2, disappeared by D_2O exchange). MS. (m/z, %): 396 (M^+ +1, 5); 277 (100); 166 (11). Anal. Calcd for $C_{19}H_{17}N_5O_3S$ (395): C, 57.71; H, 04.33; N, 17.71; S, 08.11 (%). Found**:** C, 57.81; H, 04.32; N, 17.67; S, 08.13 (%).

3-Amino-2-(4-benzylidene -3-methyl -5-oxo-4,5-dihydro- 1H-pyrazolyl)-7-methyl -5H- thiazolo [3,2-a]pyrimidin-5-one (22b)

Red powder, crystallized from dioxane, yield 69%, m.p. 220˚C; IR (KBr) cm^{-1}: 3428, 3373 (NH_2); 3021 cm^{-1} (CH-aromatic); 2930 cm^{-1} (CH-aliphatic) and 1715, 1665 cm^{-1} (2C=O). ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 01.88 ppm (s, 3H, CH_3 of pyrazolone ring); 02.19 ppm (s, 3H, CH_3 of pyrimidone ring); 05.28 ppm (s, 1H, =CH of pyrimidone ring); 07.17-07.51 ppm (m, 5H, aromatic protons); 08.60 ppm (s, 1H, =CH of benzylic proton); 09.79 ppm (br. s, 2H,NH_2,disappeared by D_2O exchange). MS. (m/z, %): 366 (M^+ +1, 20); 277 (100); 166 (13). Anal. Calcd for $C_{18}H_{15}N_5O_2S$ (365): C, 59.16; H, 04.14; N, 19.17; S, 08.78 (%). Found**:** C, 59.25; H, 04.12; N, 19.19; S, 08.77 (%).

3-Amino-7-methyl-2- (3-methyl-4- (4-nitrobenzylidene) -5-oxo-4,5- dihydro-1H-pyrazolyl) -5H-thiazolo [3,2-a]pyrimidin-5-one (22c)

Brown powder, crystallized from DMF:H_2O (1:1), yield 63%, m.p. > 300˚C; IR (KBr) cm^{-1}: 3419, 3299 cm^{-1} (NH_2); 3017 cm^{-1} (CH-aromatic); 2929 cm^{-1} (CH-aliphatic) and 1716, 1663 cm^{-1} (2C=O). ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 01.89 ppm (s, 3H, CH_3 of pyrazolone ring); 01.97 ppm (s, 3H, CH_3 of pyrimidone ring); 05.28 ppm (s, 1H, =CH of pyrimidone ring); 08.11 ppm (d, 2 H, *J* = 9 Hz, Aromatic protons); 08.34 ppm (d, 2 H, *J* = 9 Hz, Aromatic protons); 8.85 ppm (s, 1H, =CH of benzylic proton); 10.48 ppm (br. s, 2H, NH_2, disappeared by D_2O exchange). MS. (m/z, %): 411 (M^+ +1, 7); 277 (100); 166 (15). Anal. Calcd for $C_{18}H_{14}N_6O_4S$ (410): C, 52.68; H, 03.44; N, 20.48; S, 07.81 (%) Found*:* C, 52.79; H, 03.43; N, 20.53; S, 07.82 (%).

3-Amino-7-methyl-2-(3-methyl-5-oxo-4-thiophen-2-yl methylene-4,5-dihydro-1H-pyrazolyl)-5H-thiazolo[3,2-a]pyrimidin-5-one (22d)

Dark brown powder, crystallized from dioxane, yield 68%, m.p. 224-226˚C; IR (KBr) cm^{-1}: 3450, 3278 cm^{-1} (NH_2); 3015 cm^{-1} (CH-aromatic); 2924 cm^{-1} (CH-aliphatic) and 1717, 1668 cm^{-1} (2C=O). ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 01.61 ppm (s, 3H, CH_3 of pyrazolone ring); 01.97 ppm (s, 3H, CH_3 of pyrimidone ring); 05.27 ppm (s, 1H, =CH of pyrimidone ring); 07.18 ppm (m, 1H, thienyl-C_4-H); 07.60 ppm (d, 1H, *J*= 5Hz, thienyl-C_3-H), 07.77 ppm (m, 1H, thienyl-C_5-H), 8.83 ppm (s, 1H, =CH-thienyl proton), 11.07 ppm (br. s, 2H, NH_2, disappeared by D_2O exchange). MS. (m/z, %): 372 (M^+ +1, 11); 277 (100); 166 (17). Anal. Calcd for $C_{16}H_{13}N_5O_2S_2$ (371): C, 51.74; H, 03.53; N, 18.85; S, 17.27 (%). Found**:** C, 51.64; H, 03.54; N, 18.89; S, 17.23 (%).

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تشييد مشتق الثيازولو[3,2-*a*] بيريميدين-5-أون من خلال تفاعل الوعاء الواحد والذي يعمل كبادئ لتحضير مركبات متلاحمه وغير متجانسه الحلقه

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تم تشييد المركب الاساسي 3-امينو-2-هيدروكسي-7-ميثيل-ثيازولو-3,2-[*a*]بيريميدين-5-أون (5) وذلك من خلال تفاعل وعاء واحد من 2-بروموسيانواسيتاميد وإيثيل أسيتو أسيتات وثيويوريا. كما تم تحضير المركب 3-امينو-2-هيدرازينو-7-ميثيل–ثيازولوبيريميدين-5-أون (12) والذي يعمل كمفتاح تم استخدامه في تحضير سلسله من مشتقات الثيازولو بيريميدين (14,15,17,18,20,22). جميع المركبات الجديده تم اثبات تركيبها الكيميائي باستخدام الوسائل الطيفية والتحليلية المختلفه مثل (طيف الأشعة تحت الحمراء ، طيف الرنين النووي المغناطيسي ، مطياف الكتله ، البيانات التحليلية الدقيقة).