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β-Oxo anilides in Heterocyclic Synthesis: Novel Synthesis of Polyfunctionally Pyridines, Pyrimidines and Benzothiazole Derivatives

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ACETOACETANILIDE derivative 1 was reacted with aromatic aldehydes 2 to yield the arylidine derivatives 3 and 6a, b. The Hantzsch amides 7a,b were prepared by the one-pot cyclization reaction of a mixture of 2 moles of 1, aqueous ammonia and aromatic aldehydes. Treatment of 1 with ethanol containing equivalent amount of piperidine or morpholine furnished the isolable products 8a and 8b. Compound 1 underwent interamolecular heterocyclization on boiling conc. sulfuric acid, afforded 9. Also, the reaction of compound 1 with hydroxylamine hydrochloride in ethanol and sodium acetate afforded the oxime derivative 10. Furthermore, reactions of compound 1 with o-aminothiophenol furnished 11. Reactions of 1 with arylidine derivatives give compounds 13 and 16a-d. Treatment of compound 16d with elemental sulfur afforded the thieno[3,4-c]pyridine derivative 18. Treatment of 16a with hydrazine hydrate in boiling ethanol afforded the pyrazolo[3,4-b]pyridine derivatives 19. Also, compound 16a was reacted with ethylchloroacetate giving 20. Compound 20 was cyclized into the corresponding thieno[2,3-b]-pyridine derivative 21 upon boiling with ethanol containing a few drops of sodium ethoxide solution. Furthermore, compound 1 readily reacted with cyanothioacetamide to yield compound 22. Fusion of compound 1 with malononitrile over melting point without solvent in presence of ammonium acetate or refluxing in ethanolic piperidine afforded the pyridone 23a. Also, the pyridone derivative 23b was obtained by reacting compound 1 with cyanoacetamide. The reaction of acetoacetanilide 1 with ω-bromoacetophenones afforded 28a,b. Treatment of 1 with benzoyl and ethoxy carbonyl isothiocyanates afforded the pyrimidine derivatives 30a,b. The reaction of 1 with aminopyrazole gave the pyrazolopyrimidine 33. Coupling of 1 with diazonium salt of compounds 34a,b yielding 37a,b.

Keywords: Pyridines, Pyrimidines, Dyes, Pyrazolopyridines, Pyrazolopyrimidines, Triazines.

Introduction

Benzoheterocycles are potent inhibitors of the anaphylactically induced histamine release from rats peritoneal mast cells (RMC) [1]. Especially benzothiazole derivatives have been widely investigated for therapeutic uses as antiviral [2], antibacterial [3], fungicidal [4], antiallergic [1], anti-inflammatory [5, 6], as appetite depressants [7], intermediates for dyes [8], plant protectants [9] and photographic sensitizers [10].

In continuation of our previous interest in the synthesis of variety of heterocycles from readily obtainable inexpensive starting materials [11, 12], we report here on the utility of N-1, 3-benzothiazol-2-yl-3-oxobutanamide for the synthesis of some novel heterocycles incorporating a benzothiazole moiety.

Results and Discussions

β-Oxo anilide derivative 1 was reacted with aromatic aldehydes 2 in basic medium afforded the arylidine derivative 3 as literature product [13, 14]. While, the reaction proceeded by reactions of aromatic aldehydes with β-Oxo anilide derivative in glacial acetic acid

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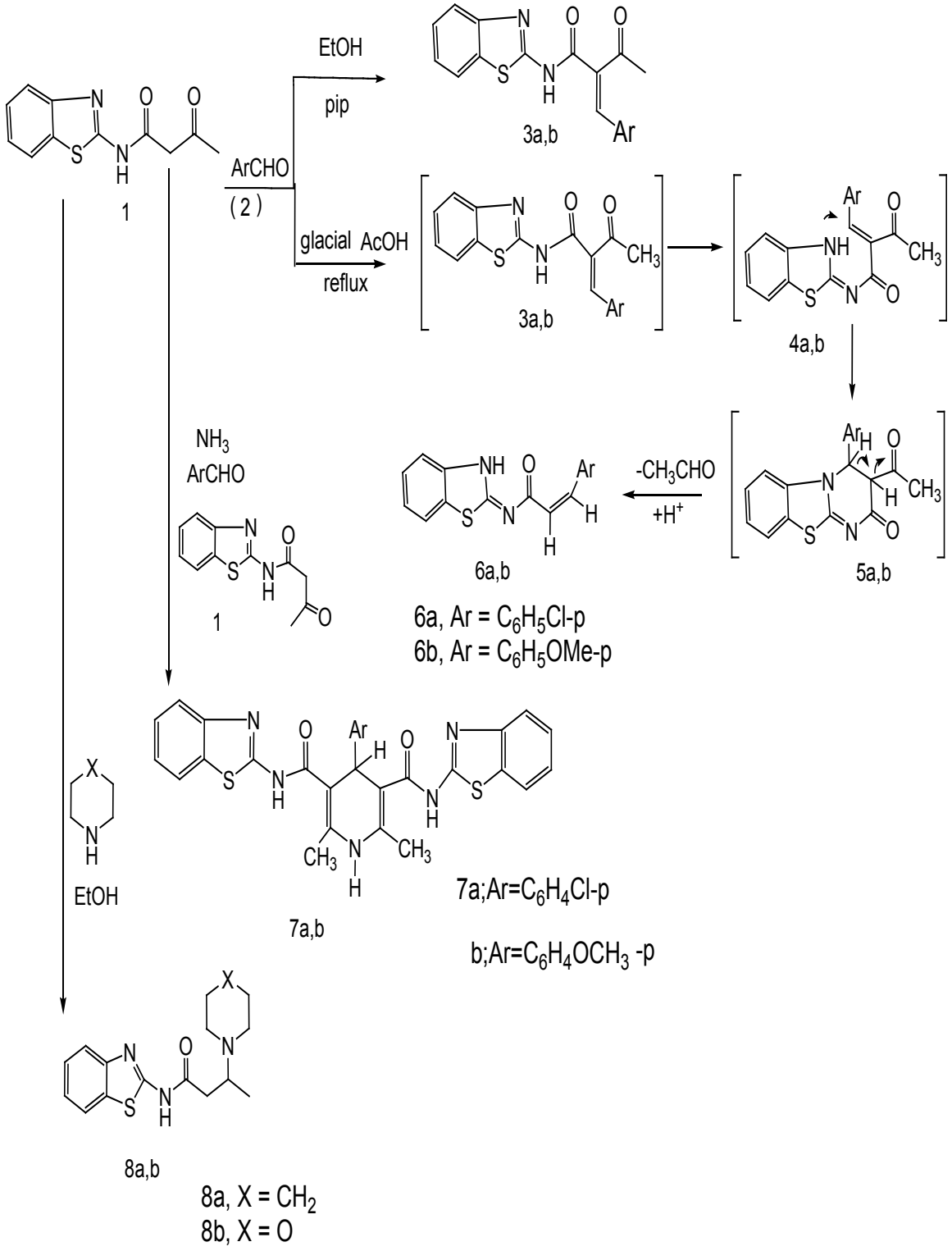
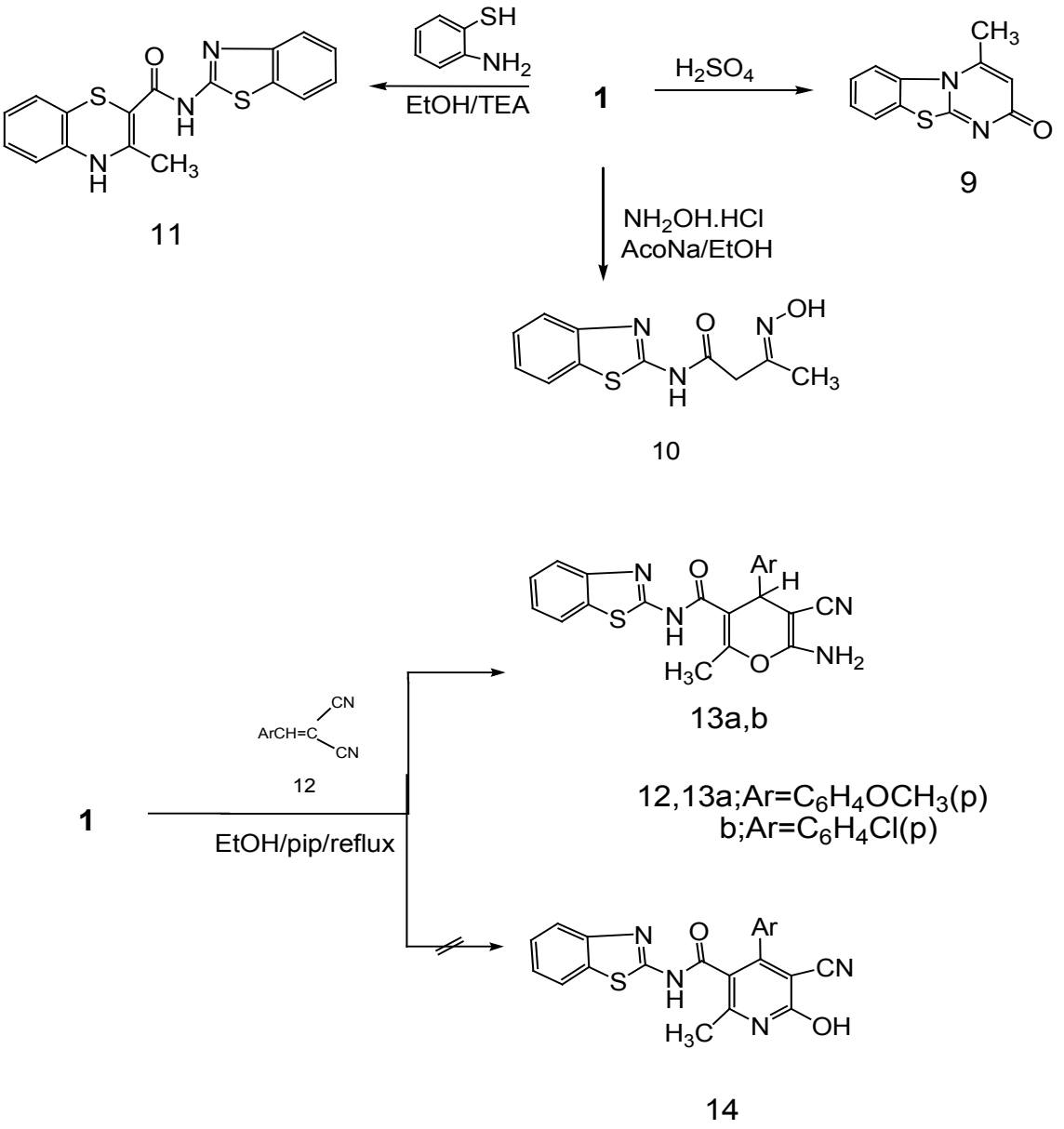
afforded a product with water and acetaldehyde elimination. This was formulated as 6a,b on the basis of its compatible spectroscopic data. Thus, the mass spectrum of 6a revealed a molecular ion peak at m/z = 312 (M^{-2}) corresponding to the molecular formula $C_{16}H_{11}ClN_2OS$. The IR spectrum showed one absorption band at 3150 cm^{-1} for NH and 1686 cm^{-1} for one carbonyl group. Also, the ^{1}H NMR spectrum of compound **6b** as an example recorded in (DMSO-d_6) revealed a singlet signal at δ 3.82 ppm corresponding to OCH_3 protons, doublet at δ 6.79-6.84 ppm corresponding to olefinic-CH, *J* = 10.4 Hz, 7.02-7.77, multiplet at δ = 7.02 – 7.77 ppm assigned for CH aromatic, doublet at δ 7.97-8.00 ppm corresponding to olefinic-CH, *J* = 10.4 Hz, and singlet signal at δ 3.82 assigned to NH and absence of the acetyl proton from the molecule. Compound **6** is assumed to be formed by the condensation of aldehydic group with methylene group via loss of water followed by cyclization to give the intermediate 5a,b. In the presence of H^+ an elimination of acetaldehyde molecule and opening the ring another one to give N-1,3-benzothiazol-2-yl-3-(4-substituted phenyl) acrylamide, (Scheme 1). The Hantzsch amides 7a,b were prepared by the one-pot cyclization reaction of a mixture of two moles of compound 1, aqueous ammonia and aromatic aldehydes [15, 16]. Compound 7 was confirmed by its analytical data (IR, ^{1}HNMR) and elemental analysis. Thus, the ^{1}HNMR spectrum of compound 7a as an example, recorded in DMSO-d_6 revealed a singlet signal at δ = 2.26 ppm assigned to $2CH_3$, singlet signal at δ = 5.37 assigned for pyridine-H, multiplet at δ = 7.14 – 7.93 ppm assigned for CH aromatic, and singlet signals at δ 9.05, 11.93 assigned to 3NH protons, (Scheme 1). Treatment of compound 1 with piperidine in ethanol furnished the isolable product 8a with water elimination. This structure has been established by elemental analysis and spectral data. It's mass spectrum showed a molecular ion peak at m/z = 301 (M^+) and its ^{1}HNMR revealed an absence of CH_2 group and revealed the presence of singlet signal at δ = 1.52 ppm assigned to CH_3, multiplet signals at δ 2.96-3.54 ppm assigned to CH_2 protons, singlet signal at δ 5.17 ppm assigned to (CH=C), and multiplet at δ 7.18-7.88 ppm assigned to Ar-H and NH protons. Similarly, when compound 1 was treated with morpholine in ethanol afforded compound 8b, (Scheme 1).

Compound 1 underwent interamolecular-heterocyclization on boiling concentrated sulfuric acid, afforded 4-methyl-2H-pyrimido[2,1-b] [1,3]-benzothiazol-2-one 9. Also, the reaction of compound 1 with hydroxylamine hydrochloride in ethanol and sodium acetate afforded the oxime derivative (10) based on its elemental analysis and analytical data IR, ^{1}HNMR. Furthermore, reactions of compound 1 with o-aminothiophenol in ethanolic triethylamine furnished N-1,3-benzothiazol-2-yl-3-methyl-4H-1,4-benzothiazine-2-carboxamide 11, [17-19], (Scheme 2). Reactions of compound 1 with arylidinemalononitrile 12 in ethanolic piperidine may form either 13 or 14. Structure 13 was preferred for the reaction product on the basis of its elemental and spectroscopic data. However, the IR spectrum of compound 13a as an example revealed the presence of an $-NH_2$ group at ν_{max} = 3430 and 3341 cm^{-1} and the absence of OH group absorption band. The ^{1}HNMR spectrum showed a singlet signal at δ = 5.71 (ppm) for 4H-pyrane whereas structure 14 would be expected to show OH protons at higher field, (Scheme 2).

The pyridinethiones 16 were obtained in quantitative yield from the reaction of acetoacetanilide 1 with arylidinecyanothioacetamide 15a-c in ethanolic piperidine rather than the isomeric structure 17. Compound 16 was confirmed based on the spectroscopic data. ^{1}HNMR spectrum of compound 16a as an example showed the presence of a singlet signals at = 12.77, 14.56 ppm assigned to (2NH) groups and absence of 4H thiopyrane would be expected at field δ 4-5 ppm. Similarly the reaction of ylidinecyanothioacetamide 15d (prepared in situ by reaction of cyanothioacetamide with acetaldehyde in ethanolic piperidine) with compound 1 afforded the pyridinethione 16d. Compound 16d was confirmed by spectroscopic data (IR, ^{1}HNMR) and its chemical reactivity of this molecule to Gewald reaction with elemental sulfur. So, further reaction of compound 16d with elemental sulfur in refluxing ethanol in the presence of little amount of triethylamine afforded the thieno[3,4-c]-pyridine derivative 18. Compound 18 was confirmed based on its elemental analysis and spectroscopic data. Thus, its IR spectrum showed disappearance of (C≡N) group at ν = 2215 cm^{-1} of compound 16d and appearance of NH_2 group at ν = 3440, 3400 cm^{-1}. Moreover, its ^{1}HNMR revealed the presence of a singlet signal at δ 6.57 ppm assigned for thiophene proton, (Scheme 3).


EtOH
pip
3a,b
ArCHO
(2)
glacial AcOH
reflux
4a,b
5a,b
-CH3CHO
+H+
6a,b
6a, Ar = C6H5Cl-p
6b, Ar = C6H5OMe-p
NH3
ArCHO
1
EtOH
7a,b
7a;Ar=C6H4Cl-p
b;Ar=C6H4OCH3 -p
8a,b
8a, X = CH2
8b, X = O

Scheme 1.

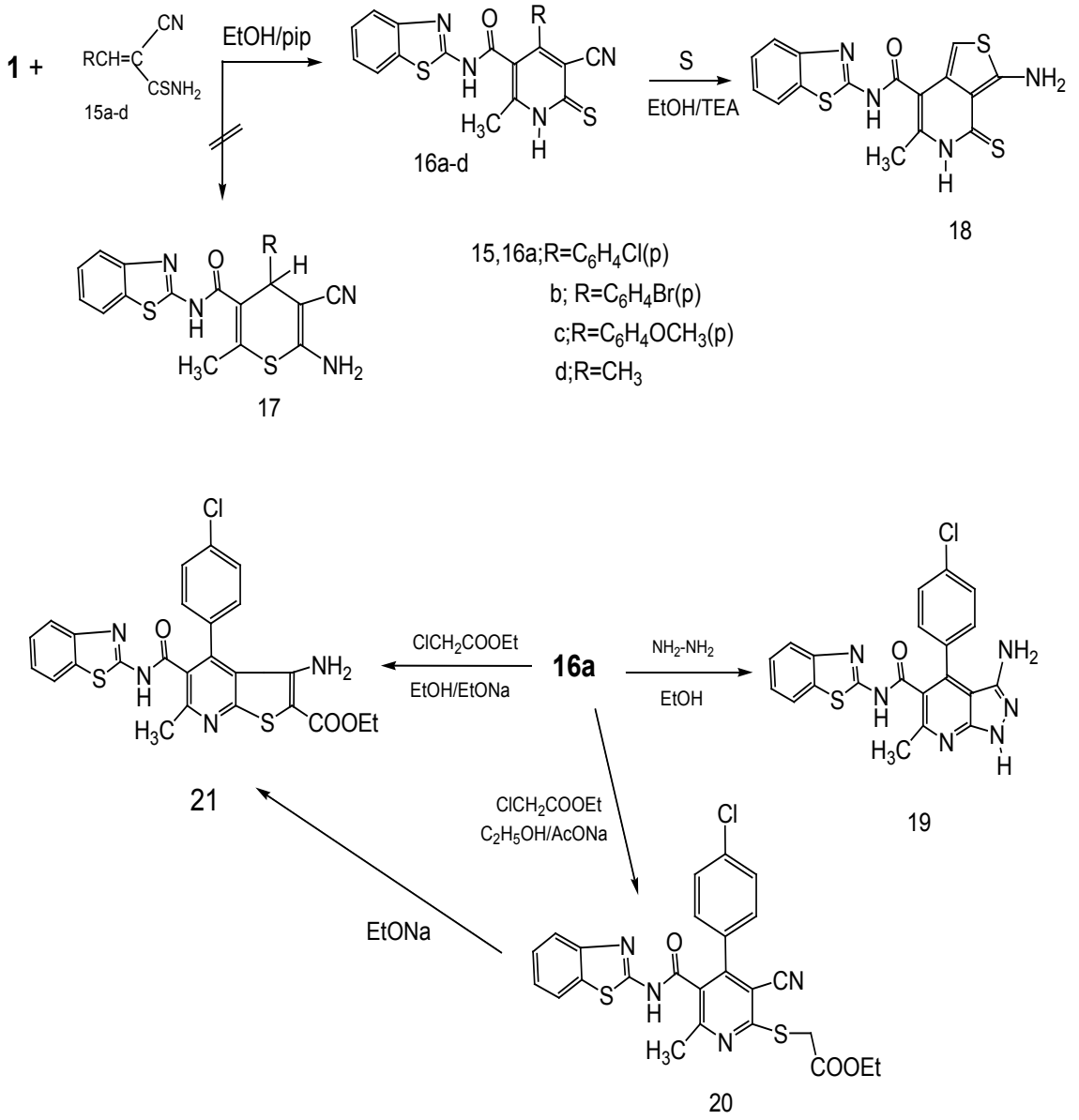


Scheme 2.

The reactivity of pyridinethione 16 towards hydrazine hydrate as binucleophilic reagent was investigated. Thus, treatment of 16a with hydrazine hydrate in boiling ethanol afforded the pyrazolo[3,4-b]pyridine derivative 19. The IR spectrum of this reaction product showed the presence of absorption bands at ν = 3426, 3400 cm^{-1} for NH_2 and 3150 cm^{-1} for NH respectively, and disappearance of the cyano function group. Furthermore, compound 16a was reacted with ethylchloroacetate in refluxing ethanol containing sodium acetate to afford [5-(1,3-Benzothiazol-2-ylcarbamoyl)-4-(4-chloro-phenyl)-3-cyano-6-methyl-pyridin-2-ylsulfanyl]-acetic acid ethyl ester 20.

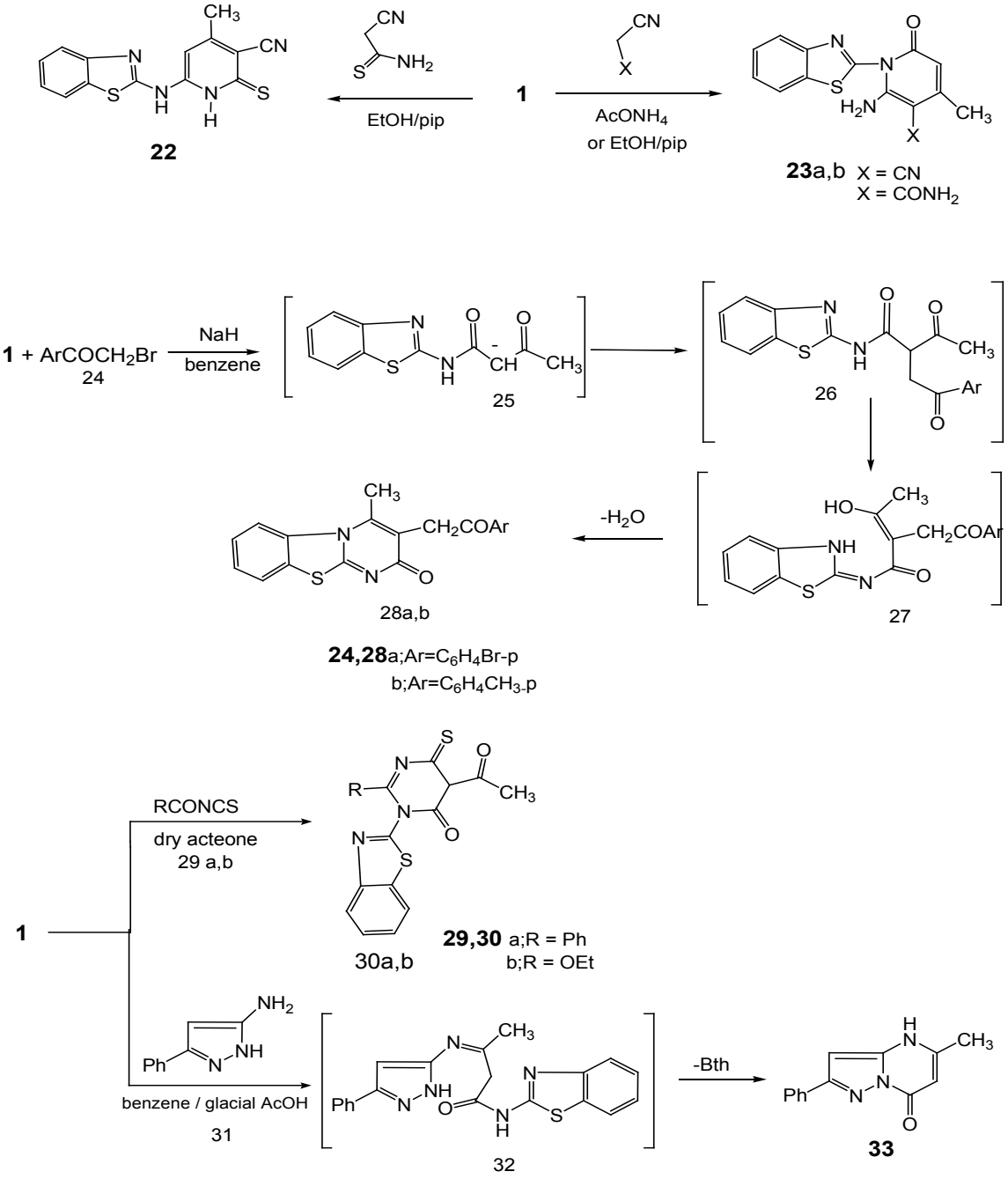
The structure of compound 20 was established based on the elemental analysis and spectral data. The IR spectrum of compound 20 exhibited the presence of the absorption band of cyano function group at ν = 2201 cm^{-1}. ^{1}HNMR spectrum of compound 20 revealed the presence of triplet at δ = 1.16 and quartet at δ = 3.60 ppm assigned to ethyl group in addition of CH_2 group at 3.59 ppm as singlet signal.

Compound 20 was cyclized into the corresponding thieno[2,3-b]-pyridine derivative 21 upon boiling with ethanol solution containing a few drops of sodium ethoxide solution. The IR spectrum of compound 21 exhibited the absence of absorption band due to cyano function group and appearance of absorption bands due to NH_2 function group at ν = 3499, 3450 cm^{-1}. ^{1}HNMR spectrum of compound 21 revealed singlet signals at δ = 0.83 ppm assigned to CH_3, triplet signals at δ =1.19 ppm assigned to CH_3, singlet signal at 2.42 ppm assigned to NH_2, quertet signals at δ = 3.67 ppm assigned to CH_2 in addition to aromatic protons and NH at δ 6.91-7.76 ppm. A solid evidence for the structure of compound 21 came from its synthesis by another route by conducting the reacting of 16a and ethyl chloroacetate in boiling solution of ethanolic sodium ethoxide (Scheme 3).



Scheme 3.

Furthermore, compound 1 readily reacted with cyanothioacetamide in refluxing ethanolic piperidine to yield the product that formulated as 6-(1,3-benzothiazol-2-ylamino)-4-methyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile 22. Compound 22 was confirmed based on spectral data. Its IR spectrum revealed the absence of carbonyl group characteristic to the acetoacetanilide and presence of (C≡N) group at ν 2203 cm^{-1}, (Scheme 4). Fusing compound 1 with malononitrile over melting point without solvent in the presence of ammonium acetate or refluxing in ethanolic piperidine afforded the pyridone (23a) in quantitative yield. Compound 23a was established based on its spectral data. Also, the pyridone derivative 23b was obtained by reacting of compound 1 with cyanoacetamide under the same reaction conditions, (Scheme 4).

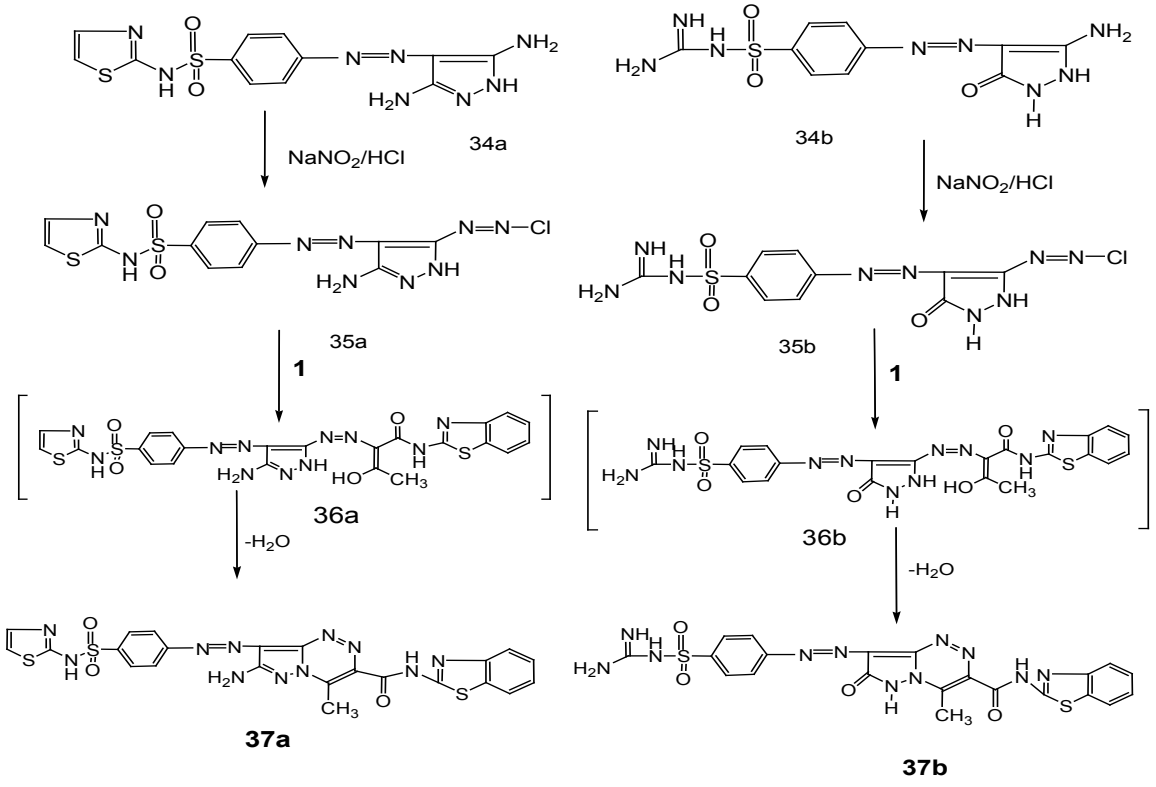


Scheme 4.

The reaction of compound 1 with ω-bromoacetophenones 24 afforded pyrimido[2,1-b][1,3]-benzothiazol-2-one derivatives 28a,b. Compound 28 was established by analytical data (IR, ^{1}HNMR) and elemental analysis. Compound 28 was assumed to be proceeding via the first step involves a carbon carbon bond forming reaction by the attack of carbanion generated by treatment of acetoacetanilide 1 with sodium hydride in dry benzene on the bromomethyl to obtain the corresponding sodium salt. This in turn when treated with ω-bromoacetophenones 24 afforded the intermediate 26 which cyclized in the reaction medium by loss of H_2O to the final product 28, (Scheme 4).

Treatment of 1 with benzoyl and ethoxycarbonyl isothiocyanate 29a,b (prepared in situ) in dry acetone afforded the pyrimidine derivatives 30a,b. Compound 30 was confirmed by spectral data, IR, ^{1}HNMR and elemental analysis, (Scheme 12). The reaction of compound 1 with aminopyrazole 33 in benzene containing glacial acetic acid afforded products via water and 2-aminobenzo-thiazole molecule elimination. The pyrazolopyrimidine 33 was established as reaction product based on spectral data. Thus, the mass spectrum revealed a molecular ion peak at m/z = 225 (M^+) corresponding to the molecular formula $C_{13}H_{11}N_3O$. Also, the ^{1}HNMR spectrum recorded in (DMSO-d_6) exhibited a singlet signal at δ = 2.31 ppm assigned to CH_3, singlet signal at δ = 5.61 ppm assigned to pyrazole-H, singlet signal at δ = 6.58 ppm assigned to pyrimidine-H, multiplet signals at δ = 7.40-8.00 ppm assigned to Ar-H, and hump signal at δ = 12.57 ppm assigned to NH. Compound 33 is assumed to be formed via initial condensation of exocyclic amino function in 31 with the carbonyl group in compound 1 to give the intermediate 32 which readily cyclized to the final isolable product pyrazolo[1,5-a]pyrimidine 33, (Scheme 4).

Coupling of compound 1 with diazonium salt of compounds 34a,b yielding the coupling products. 7-Amino-4-methyl-8-[4-(thiazol-2-yl-sulfamoyl)-phenylazo]-pyrazolo[5,1-c][1,2,4] triazine-(1,3-benzothiazol-2-yl)-3-carboxamide 37a and 4-Methyl-7-oxo-8-[4-(guanidin-2-yl-sulfamoyl)-phenylazo]-pyrazolo[5,1-c]-[1,2,4] triazine-(1,3-benzothiazol-2-yl)-3-carboxamide 37b, in good yield via the intermediates 36a,b respectively, (Scheme 5).



Scheme 5.

Materials and Methods

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ at 200, 400 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analysis was carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Microanalytical Research Center, Assiut University.

Preparation of compounds (6a,b): *General procedure*

To a solution of acetoacetanilide 1 (0.01 mole) in glacial acetic acid (30 ml), aromatic aldehyde (0.01 mole) was added. The reaction mixture was refluxed for 24 hrs and left to cool. The solid product was collected by filteration and recrystallized from the proper solvent to give 6a,b.

N-1,3-Benzothiazol-2-yl-3-(4-chlorophenyl) acrylamide (6a)

It was obtained as a pale yellow crystals from ethanol; yield 83%; m.p. 280-2°C; IR (KBr) ν cm^{-1} 3150 (NH), 3050 (CH-arom), 1686 (C=O); ^1H NMR (DMSO-d_6) δ = 6.9-7.0 (d, 1H, CH-olefinic), 7.3-7.9 (m, 8H, Ar-H), 8.0-8.1 (d, 1H, CH-olefinic), 12.63 (s, 1H, NH); MS: m/z 312 (M-2). Found; C, 61.07; H, 3.33; N, 8.92; cald. For $C_{16}H_{11}ClN_2OS$ (314.79); C, 61.05; H, 3.52; N, 8.90.

N-1,3-Benzothiazol-2-yl-3-(4-methoxyphenyl) acrylamide (6b)

It was obtained as colorless crystals from ethanol; yield 77%; m.p. 256-8°C; IR (KBr) ν cm^{-1} 3174 (NH), 3062 (CH-arom), 2957 (CH-aliph), 1680 (C=O); ^1H NMR (DMSO-d_6) δ = 3.82 (s, 3H, OCH_3), 6.79-6.84 (d, 1H, CH-olefinic) J = 10.4 Hz, 7.02-7.77 (m, 8H, Ar-H), 7.97-8.00 (d, 1H, CH-olefinic), 12.5 (s, 1H, NH). Found; C, 65.77; H, 4.54; N, 9.02; cald. For; $C_{17}H_{14}N_2O_2S$ (310.37); C, 65.79; H, 4.55; N, 9.03.

Preparation of compounds (7a,b): *General procedure*

A mixture of acetoacetanilide 1 (0.02 mole), 20% aqueous NH_3 (1.2 ml) and aromatic aldehydes (0.01 mole) in (20 ml) EtOH was refluxed for 12 hr. The solid product which produced on hot was collected by filteration and recrystallized from the proper solvent to give 7a,b.

4-(4-Chloro-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxamide bis(1,3-benzothiazol-2yl) (7a)

It was obtained as yellow crystals from Dioxane/EtOH; yield 83%; m.p. 290-2°C; IR (KBr) ν cm^{-1} 3330, 3230 (2NH), 3060 (CH-arom), 2980 (CH-aliphatic), 1657 (C=O); ^1H NMR (DMSO-d_6) δ = 2.26 (s, 6H, $2CH_3$), 5.37 (s, 1H, pyridine-H), 7.14-7.93 (m, 12H, Ar-H), 9.05 (s, 1H, NH), 11.93 (s, 2H, 2NH). Found; C, 60.89; H, 3.89; N, 12.25; cald. For $C_{29}H_{22}ClN_5O_2S_2$ (572.11); C, 60.88; H, 3.88; N, 12.24.

4-(4-Methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxamide bis(1,3-benzothiazol-2-yl) (7b)

It was obtained as pale yellow crystals from benzene; yield 67%; m.p. 158-60°C; IR (KBr) ν cm^{-1} 3320, 3250 (2NH), 2956 (CH-aliphatic), 1668 (C=O). Found; C, 63.48; H, 4.45; N, 12.36; cald. For $C_{30}H_{25}N_5O_3S_2$ (567.69); C, 63.47; H, 4.44; N, 12.34.

Preparation of compounds (8a,b): *General procedure*

A solution of acetoacetanilide **1** in ethanol (30 ml) was treated with a few drops of piperidine (0.5 ml), or morpholin (0.5 ml). The solution was heated under reflux for 1 hr. The solid product which produced on hot was collected by filteration and recrystallized from the proper solvent to give 8a,b.

N-1,3-Benzothiazol-2-yl-3-piperidin-1-ylbut-2-enamide (8a)

It was obtained as yellow crystals from ethanol; yield 76%; m.p. 232-4°C; IR (KBr) ν cm^{-1} 3200 (NH), 3025 (CH-arom), 2937 (CH-aliph), 1659 (C=O); ^1H NMR (DMSO-d_6) δ = 1.52 (s, 3H, CH_3), 2.96-3.54 (m, 10H, $5CH_2$), 5.17 (s, 1H, CH=C), 7.18-7.88 (m, 5H, Ar-H and NH); MS: m/z = 301 (M^+). Found; C, 63.77; H, 6.36; N, 13.95; cald. For $C_{16}H_{19}N_3OS$ (301.41); C, 63.67; H, 6.35; N, 13.94.

N-1,3-Benzothiazol-2-yl-3-morpholin-4-yl-but-2-enamide (8b)

It was obtained as colorless crystals from ethanol; yield 81%; m.p. 222°C; IR (KBr) ν cm^{-1} 3200 (NH), 2918 (CH-aliph), 1655 (C=O); ^1H NMR (DMSO-d_6) δ = 2.48 (s, 3H, CH_3), 3.27-3.67 (m, 8H, $4CH_2$), 5.19 (s, 1H, CH=C), 7.21-7.90 (m, 4H, Ar-H), 11.52 (s, 1H, NH). Found; C, 59.39; H, 5.65; N, 13.86; cald. For $C_{15}H_{17}N_3O_2S$ (303.39); C, 59.39; H, 5.67; N, 13.85.

4-Methyl-2H-pyrimido[2,1-b][1,3]-benzothiazol-2-one (9)

Acetoacetanilide 1 (2 gm) was heated under reflux in conc. sulfuric acid for 10 minutes at 250°C. The reaction mixture was left to stand, and poured into H_2O (100 ml) the solid product was collected by filteration and recrystallized from DMF/EtOH to give (**9**; 62%) as brown crystals; m.p. >300°C; IR (KBr) ν cm^{-1} 3042 (CH-arom), 2969 (CH-aliph), 1649 (C=O). Found; C, 61.08; H, 3.72; N, 12.94; cald. For $C_{11}H_8N_2OS$ (216.26); C, 61.09; H, 3.73; N, 12.95.

N-1,3-Benzothiazol-2-yl-3-(hydroxyimino) butanamide (10)

To a solution of acetoacetanilide 1 (0.01 mole), hydroxylamine hydrochloride (0.01 mole), sodium acetate (0.5 gm), H_2O (1 ml) and 20 ml of ethanol was refluxed for 3 hrs. Then left to cool, and poured into crushed ice. The solid product was collected by filteration and recrystallized from Dioxane/EtOH to give (**10**, 72%) as brown crystals; m.p. >300°C; IR (KBr) ν cm^{-1} 3440 (OH), 3348 (NH), 2921 (CH-aliph), 1650 (C=O); ^{1}H NMR (DMSO-d_6) δ = 1.23 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 7.30-7.41 (m, 5H, 4Ar-H + NH), 8.12 (hump, 1H, OH). Found $C_{11}H_{11}N_3O_2S$ (249.29); C, 53.02; H, 4.46; N, 16.88; cald. For; C, 53.00; H, 4.45; N, 16.86.

N-1,3-Benzothiazol-2-yl-3-methyl-4H-1,4-benzothiazine-2-carboxamide (11)

To a solution of 1 (0.01 mole) and 2.5 ml (0.032 mole) of triethylamine in ethanol (30 ml), o-aminothiophenol (0.01 mole) in 7.5 ml of ethanol was added at 20°C. The solution was kept at room temperature for 6 h, then poured into water. The solid product was collected by filteration and recrystallized from ethanol to give (11, 81%) as orange crystals; m.p. 202°C; IR (KBr) ν cm^{-1} 3255 (NH), 3050 (CH-arom), 1660 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.28 (s, 3H, CH_3), 6.74-7.93 (m, 9H, Ar-H and NH), 8.94 (hump, 1H, NH). Found; C, 60.17; H, 3.87; N, 12.39; cald. For $C_{17}H_{13}N_3OS_2$ (339.44); C, 60.15; H, 3.86; N, 12.38.

Preparation of compounds (13a,b):*General procedure*

A mixture of 1 (0.01 mole), α-cyano-4-substituted cinnamonitrile (0.01 mole) in ethanol (30 ml) was treated with a few drops of piperidine and heated under reflux for 8 hrs. The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and recrystallized from the proper solvent to give 13a,b.

6-Amino-N-1,3-benzothiazol-2-yl-5-cyano-4-(4-methoxy-phenyl)-2-methyl-4H-pyran-3-carboxamide (13a)

It was obtained as yellow crystals from ethanol; yield 81%; m.p. 264-66°C; IR (KBr) ν cm^{-1} 3430, 3341 (NH_2), 3086 (CH-arom), 2917 (CH-aliph), 2202 (C≡N), 1682 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.19 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.71 (s, 1H, 4H-pyrane), 7.52-8.18 (m, 11H, Ar-H, NH_2 and NH). Found; C, 60.15; H, 4.35; N, 13.40; cald. For $C_{22}H_{18}N_4O_3S$ (418.48); C, 63.14; H, 4.34; N, 13.39.

6-Amino-N-1,3-benzothiazol-2-yl-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxamide (13b)

It was obtained as brown crystals from ethanol; yield 86%; m.p. 184°C; IR (KBr) ν cm^{-1} 3420, 3331, 3108 (NH_2, NH), 2924 (CH-aliph), 2200 (C≡N), 1677 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.20 (s, 3H, CH_3), 5.72 (s, 1H, 4H-pyrane), 7.29-8.18 (m, 11H, Ar-H, NH_2 and NH). Found; C, 59.65; H, 3.59; N, 13.26; cald. For $C_{21}H_{15}ClN_4O_2S$ (422.90); C, 59.64; H, 3.58; N, 13.25.

Preparation of compounds **(16a-d):** *General procedure*

A mixture of 1 (0.01 mole), arylidinecyanothioacetamide (0.01 mole) in ethanol (30 ml) was treated with a few drops of piperidine and refluxed for 5 hrs. The reaction mixture then left to cool, poured into crushed ice and acidified with HCl. The solid product was collected and recrystallized from the proper solvent to give 16a-d.

N-1,3-Benzothiazol-2-yl-4-(4-chlorophenyl)-5-cyano-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (16a)

It was obtained as yellow crystals from ethanol; yield 86%; m.p. 210°C; IR (KBr) ν cm^{-1} 3217 (NH), 3058 (CH-arom), 2973 (CH-aliph), 2200 (CN), 1673 (C=O); ^{1}H NMR (DMSO-d_6) δ = 1.92 (s, 3H, CH_3), 7.27-7.95 (m, 8H, Ar-H), 12.77 (s, 1H, NH), 14.56 (s, 1H, NH). Found; C, 57.74; H, 3.01; N, 12.83; cald. For $C_{21}H_{13}ClN_4OS_2$ (436.94); C, 57.73; H, 3.00; N, 12.82.

N-1,3-Benzothiazol-2-yl-4-(4-bromophenyl)-5-cyano-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (16b)

It was obtained as pale yellow crystals from benzene; yield 81%; m.p. 198-200°C; IR (KBr)

ν cm^{-1} 3380, 3215 (2NH), 3056 (CH-arom), 2947 (CH-aliph), 2172 (C≡N), 1654 (C=O). Found; C, 52.42; H, 2.73; N, 11.65; cald. For $C_{21}H_{13}BrN_4OS_2$ (481.40); C, 52.40; H, 2.72; N, 11.64.

N-1,3-Benzothiazol-2-yl-5-cyano-4-(4-methoxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (16c)

It was obtained as yellow crystals from benzene; yield 85%; m.p. 250°C; IR (KBr) ν cm^{-1} 3447, 3182 (2NH), 3065 (CH-arom), 2959 (CH-aliph), 2230 (C≡N), 1686 (C=O). ^{1}H NMR (DMSO-d_6) δ = 2.43 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 6.97-7.96 (m, 10H, Ar-H + 2NH). Found; C, 61.08; H, 3.72; N, 12.94; cald. For $C_{22}H_{16}N_4O_2S_2$ (432.53); C, 61.09; H, 3.73; N, 12.95.

N-1,3-Benzothiazol-2-yl-5-cyano-2,4-dimethyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (16d)

It was obtained as brown crystals from ethanol; yield 57%; m.p. 228-230°C; IR (KBr) ν cm^{-1} 3422 (NH), 3062 (CH-arom), 2929 (CH-aliph), 2215 (CN), 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ = 0.73 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 6.74-7.29 (m, 6H, Ar-H and 2NH). Found; C, 56.46; H, 3.57; N, 16.47; cald. For $C_{16}H_{12}N_4OS_2$ (340.43); C, 56.45; H, 3.55; N, 16.46.

3-Amino-N-1,3-benzothiazol-2-yl-6-methyl-4-thioxo-4,5-dihydrothieno[3,4-c]pyridine-7-*carboxamide* (18)

Equimolar amounts of 16d (0.01 mole) and elemental sulfur (0.01 mole) in ethanol (30 ml) were treated with triethylamine (0.5 ml) and refluxed for 4 hrs. The solid formed after cooling was collected and recrystallized from benzene to give (18; 60%) as green crystals; m.p. 180°C; IR (KBr) ν cm^{-1} 3440, 3400 (NH_2), 3180, 3120 (2NH), 3050 (CH-arom), 2937 (CH-aliph), 1690 (C=O); ^{1}H NMR (DMSO-d_6) δ = 1.71 (s, 3H, CH_3), 6.45 (s, 2H, NH_2), 6.57 (s, 1H, thiophene-H), 6.86-6.87 (m, 5H, Ar-H and NH), 9.84 (s, 1H, NH). Found; C, 51.60; H, 3.27; N, 15.05; cald. For $C_{16}H_{12}N_4OS_3$ (372.49); C, 51.59; H, 3.25; N, 15.04.

3-Amino-N-1,3-benzothiazol-2-yl-4-(4-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b] pyridine-5-carboxamide (19)

A solution of compound 16a (0.01 mole) in ethanol (10 ml) was treated with an excess of hydrazine hydrate (10 ml). The mixture was heated under reflux for 12 hrs, and left to stand. Poured on ice cold water and acidified with HCl. The solid product so formed was obtained by filteration and recrystallized from ethanol to give (19; 82%) as brown crystals; m.p. 154-6°C; IR (KBr) ν cm^{-1} 3426, 3400 (NH_2), 3150 (NH), 3050 (CH-arom), 2927 (CH-aliph), 1677 (C=O); ^{1}H NMR ($CDCl_3$) δ = 1.16 (s, 3H, CH_3), 3.68 (s, 2H, NH_2), 6.67-7.77 (m, 10H, Ar-H and 2NH). Found; C, 58.01; H, 3.49; N, 19.33; cald. For $C_{21}H_{15}ClN_6OS$ (434.91); C, 58.00; H, 3.48; N, 19.32.

[5-(1,3-Benzothiazol-2-yl-carbamoyl)-4-(4-chlorophenyl)-3-cyano-6-methyl-pyridin-2-yl-sulfanyl]-acetic acid ethyl ester (20)

To a solution of 16a (0.01 mole) in ethanol, ethylchloroacetate (0.01 mole) and sodium acetate (0.5 g) were added. The mixture was refluxed for 4 hrs, cooled, poured into crushed ice and acidified with HCl. The precipitate formed was collected and recrystallized from ethanol to give (**20**; 73%) as pale yellow crystals; m.p. 158-60°C; IR (KBr) ν cm^{-1} 3258 (NH), 3061 (CH-arom), 2924 (CH-aliph), 2201 (C≡N), 1734, 1667 (2C=O); ^{1}H NMR ($CDCl_3$) δ = 1.10 (s, 3H, CH_3), 1.16 (t, 3H, CH_3), 3.59 (s, 2H, CH_2), 3.60 (q, 2H, CH_2), 7.10-7.70 (m, 8H, Ar-H), 8.90 (s, 1H, NH). Found; C, 57.43; H, 3.67; N, 10.72; cald. For $C_{25}H_{19}ClN_4O_3S_2$ (523.04); C, 57.41; H, 3.66; N, 10.71.

3-Amino-5-(1,3-benzothiazol-2-yl-carbamoyl)-4-(4-chloro-phenyl)-6-methyl-thieno[2,3-b] pyridine-2-carboxylic acid ethyl ester (21):

Method (A)

To a solution of sodium ethoxide, a solution of 20 (0.01 mole) in ethanol (20 ml) was added. The reaction mixture was refluxed for 3 hrs. After cooling the reaction mixture was poured into cold water (50 ml) and acidified with HCl. The product formed was collected by filteration and recrystallized from ethanol to give (**21**; 65%) as yellow crystals; m.p. 186-88°C; IR (KBr) ν cm^{-1} 3499, 3450 (NH_2), 3340 (NH), 2929 (CH-aliph), 1683 (C=O); ^{1}H NMR ($CDCl_3$) δ = 0.83 (s, 3H, CH_3), 1.19 (t, 3H, CH_3), 2.42 (s, 2H, NH_2), 3.67 (q, 2H, CH_2), 6.91-7.76 (m, 9H, Ar-H and NH). Found; C, 57.43; H, 3.67; N, 10.72; cald. For $C_{25}H_{19}ClN_4O_3S_2$ (523.04); C, 57.41; H, 3.66; N, 10.71.

Method (B)

To a solution of 16a (0.01 mole) in ethanol, ethylchloroacetate (0.01 mole) and sodium ethoxide (0.01 mole sodium in 10 ml ethanol) were added. The reaction mixture was refluxed for 12 hrs, then left to stand, poured into cold water (50 ml) and acidified with HCl. The product formed was collected by filteration and recrystallized from ethanol to give (21; 77%) as yellow crystals.

6-(1,3-Benzothiazol-2-ylamino)-4-methyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile (22):

A mixture of 1 (0.01 mole) and cyanothioacetamide (0.01 mole) in ethanol (30 ml) was treated with a few drops of piperidine and refluxed for 8 hrs. The solid product was collected by filteration and recrystallized from ethanol to give (22; 59%) as brown crystals; m.p. 190°C; IR (KBr) ν cm^{-1} 3327, 3199 (2NH), 3059 (CH-arom), 2928 (CH-aliph), 2203 (C≡N); ^{1}H NMR (DMSO-d_6) δ = 1.27 (s, 3H, CH_3), 7.27 (s, 1H, pyridine-H), 7.42-7.79 (m, 6H, Ar-H + 2NH). Found; C, 56.36; H, 3.39; N, 18.79; cald. For $C_{14}H_{10}N_4S_2$ (298.39); C, 56.35; H, 3.38; N, 18.78.

Preparation of compounds (23a,b): *General procedure*

Method (A)

A mixture of 1 (0.01 mole), appropriate active methylene reagent (malononitrile or cyanoacetamide) (0.01 mole) and ammonium acetate (0.5 gm) was fused for 30 minutes at 140°C. The reaction mixture was left to stand, then triturated with ethanol. The solid product so formed was collected by filteration and recrystallized from the proper solvent to give 23a,b.

Method (B)

A mixture of 1 (0.01 mole), appropriate active methylene reagent (malononitrile or cyanoacetamide) (0.01 mole) in ethanol (30 ml) was treated with a few drops of piperidine and refluxed for 12 hrs, then left to cool. The solid product formed was filtered off and crystallized from the proper solvent to give 23a,b.

2-Amino-1-(1,3-benzothiazol-2-yl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (23a)

It was obtained as brown crystals from dioxane/ethanol; yield 74%; m.p. 268-70°C; IR (KBr) ν cm^{-1} 3350 (NH_2), 3090 (CH-arom), 2200 (C≡N), 1660 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.20 (s, 3H, CH_3), 5.72 (s, 2H, NH_2), 7.54-8.19 (m, 5H, Ar-H + pyridine-H); MS: m/z = 282 (M^+). Found; C, 59.57; H, 3.58; N, 19.85; cald. For $C_{14}H_{10}N_4OS$ (282.33); C, 59.56; H, 3.57; N, 19.84.

2-Amino-1-(1,3-benzothiazol-2-yl)-4-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (23b):

It was obtained as orang crystals from ethanol; yield 70%; m.p. 180°C; IR (KBr) ν cm^{-1} 3400, 3350 (NH_2), 2930 (CH-aliph), 1720, 1640 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 1.25 (s, 3H, CH_3), 5.23 (s, 2H, NH_2), 5.39 (hump, 2H, NH_2), 6.17 (s, 1H, pyridine-H), 7.12-8.32 (m, 4H, Ar-H). Found; C, 55.98; H, 4.02; N, 18.64; cald. For $C_{14}H_{12}N_4O_2S$ (300.34); C, 55.99; H, 4.03; N, 18.65.

Preparation of compounds (28a,b): *General procedure*

A mixture of acetoacetanilide 1 (0.01 mole), ω-bromoacetophenone (0.01 mole) and sodium hydride (0.31 g, 0.01 mole) in dry benzene (20 ml) was stirred for 2 hr at 40°C. The separated solid was filtered off, treated with dil HCl (2:1), washed with excess of water and recrystallized from the proper solvent to give (28a,b).

4-Methyl-3-[2-(4-Bromophenyl)-2-oxo-ethyl]-2H-pyrimido-[2,1-b][1,3]-benzothiazol-2-one (28a).

It was obtained as red crystals from ethanol; yield 67%; m.p. 192-4°C; IR (KBr) ν cm^{-1} 3080 (CH-arom), 2980 (CH-aliph), 1669 (C=O); ^{1}H NMR ($CDCl_3$) δ = 1.27 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 6.92-7.78 (m, 8H, Ar-H). Found; C, 55.23; H, 3.19; N, 6.79; cald. For $C_{19}H_{13}BrN_2O_2S$ (413.30); C, 55.22; H, 3.17; N, 6.78.

4-Methyl-3-[2-(4-methylphenyl)-2-oxo-ethyl]-2H-pyrimido-[2,1-b][1,3]-benzothiazol-2-one (28b)

It was obtained as brown crystals from ethanol; yield 77%; m.p. 138-40°C; IR (KBr) ν cm^{-1} 3040 (CH-arom), 2922 (CH-aliph), 1680 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.20 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.37 (s, 2H, CH_2), 7.26-7.96 (m, 8H, Ar-H). Found; C, 68.96; H, 4.65; N, 8.06; cald. For $C_{20}H_{16}N_2O_2S$ (348.43); C, 68.95; H, 4.63; N, 8.04.

Preparation of compounds (30a,b): *General procedure*

To a solution of compound **1** (0.01 mole) in dry acetone (50 ml), benzoyl or ethoxy carbonyl isothiocyanate (0.01 mole) was added. The reaction mixture was heated under reflux for 12 hrs, then left to cool. The solid product was collected by filteration and recrystallized from the proper solvent to give (30a,b).

5-Acetyl-3-(1,3-benzothiazol-2-yl)-2-phenyl-6-thioxo-5,6-dihydro-pyrimidin-4(3H)-one (30a):

It was obtained as pale yellow crystals from ethanol; yield 62%; m.p. 190°C; IR (KBr) ν cm^{-1} 3002 (CH-arom), 1713, 1668 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 2.14 (s, 3H, $COCH_3$), 7.29-7.89 (m, 9H, Ar-H), 7.97 (s, 1H, pyrimidin-H). Found; C, 60.15; H, 3.46; N, 11.08; cald. For

$C_{19}H_{13}N_3O_2S_2$ (379.46); C, 60.14; H, 3.45; N, 11.07.

5-Acetyl-3-(1,3-benzothiazol-2-yl)-2-ethoxy-6-thioxo-5,6-dihydropyrimidin-4 (3H)-one (30b):

It was obtained as brown crystals from Dioxane/EtOH; yield 71%; m.p. 298-300°C; IR (KBr) ν cm^{-1} 3080 (CH-arom), 2988 (CH-aliph), 1720, 1658 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 1.26 (t, 3H, CH_3), 2.06 (s, 3H, $COCH_3$), 4.23 (q, 2H, CH_2), 7.25-8.01 (m, 5H, Ar-H + pyrimidin-H). Found; C, 51.85; H, 3.76; N, 12.08; cald. For $C_{15}H_{13}N_3O_3S_2$ (347.42); C, 51.86; H, 3.77; N, 12.09.

5-Methyl-2-phenyl-pyrazolo[1,5-a]pyrimidin-7-one (33)

A mixture of 1 (0.01 mole) and (0.01 mole) of aminopyrazole derivatives in benzene (30 ml) containing glacial acetic acid (10 ml) was heated under reflux for 3 hrs. The solvent was then evaporated and the resulting solid product was filtered off and recrystallized from DMF/EtOH to give (33; 69%) as colorless crystals; m.p. >300°C; IR (KBr) ν cm^{-1} 3534 (NH), 3060 (CH-arom), 2892 (CH-aliph), 1662 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.31 (s, 3H, CH_3), 5.61 (s, 1H, pyrazole-H), 6.58 (s, 1H, pyrimidine-H), 7.40-8.00 (m, 5H, Ar-H), 12.57 (hump, 1H, NH); MS: m/z = 225 (M^+). Found; C, 69.34; H, 4.93; N, 18.66; cald. For $C_{13}H_{11}N_3O$ (225.25); C, 69.32; H, 4.92; N, 18.65.

Preparation of compounds (37a,b): *General procedure*

A cold solution of diazonium aminopyrazole salt (10 mmol) (perpared by adding a solution of sodium nitrite (1.5 gm into 10 ml H_2O) to cold solution of amine hydrochloride (0.1 mole in 10 ml concentrated HCl) was stirring in ice bath. The resulting solution of diazonium salt was then added to cold solution of compound 1 (0.01 mole) in ethanol (30 ml) containing 2 gm of sodium acetate at 0°C for 1 hr. The resulting solid was washed with water and recrystallized from the proper solvent to give 37a,b.

7-Amino-4-methyl-8-[4-(thiazol-2-yl-sulfamoyl)-phenylazo]-pyrazolo[5,1-c][1,2,4]triazine-(1,3-benzothiazol-2-yl)-3-carboxamide (37a)

It was obtained as brown crystals from ethanol; yield 77%; m.p. 186°C; IR (KBr) ν cm^{-1} 3300, 3280 (NH_2), 3220, 3146 (2NH), 3020 (CH-arom), 1659 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.22 (s, 3H, CH_3), 6.82-8.05 (m, 12H, Ar-H, thiazole-H and NH_2), 12.72 (hump, 1H, NH), 13.21 (s, 1H, NH). Found; C, 46.70; H, 2.92; N, 26.05; cald. For $C_{23}H_{17}N_{11}O_3S_3$ (591.66); C, 46.69; H, 2.90; N, 26.04.

4-Methyl-7-oxo-8-[4-(guanidin-2-yl-sulfamoyl)-phenylazo]-pyrazolo[5,1-c][1,2,4]triazine-(1,3-benzothiazol-2-yl)-3-carboxamide (37b)

It was obtained as brown crystals from ethanol; yield 71%; m.p. 270°C; IR (KBr) ν cm^{-1} 3444, 3425 (NH_2), 3329, 3220 (2NH), 2980 (CH-aliph), 1636 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.48 (s, 3H, CH_3), 6.70 (hump, 2H, NH_2), 7.34-8.05 (m, 10H, Ar-H and 2NH), 12.65 (s, 1H, NH), 13.26 (s, 1H, NH). Found; C, 45.74; H, 3.13; N, 27.95; cald. For $C_{21}H_{17}N_{11}O_4S_2$ (551.57); C, 45.73; H, 3.11; N, 27.93.

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بيتا- اوكسو انيليدات فى تشييد الحلقات الغير متجانسه: تشييد فريد لمشتقات البريدين, البيريميدين و البنزوثيازول متعدد الوظائف

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تم تشييد فريد لمشتقات البريدين , البيريميدين و البنزوثيازول متعدد الوظائف و على سبيل المثال مفاعلة مشتقات الاسيتواسيتانليدات مع الامينوبيرازول للحصول على البيرازولوبيريميدين و تم إثبات المركبات الجديدة التى تم الحصول عليها بأستخدام التحاليل الدقيقة و الاطياف الضوئية المختلفة.