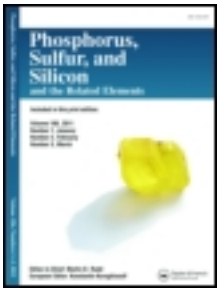

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A Convenient and Facile Synthesis of New Thiazole Derivatives

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A Convenient and Facile Synthesis of New Thiazole Derivatives

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4-Chloro-2,3-dihydrothiazole-5-carboxaldehyde reacted with some nucleophilic reagents such as hydrazine hydrate, phenyl hydrazine, urea, thiourea, semicarbazide, cyanoacetamide, cyanothio-acetamide, cyanoacetohydrazide, 2-phenylenediamine, 2-aminophenol, 5-amino[1,2,4]triazole and 3-aminopyrazole in ethanol solution at reflux in the presence of catalytic amount of triethylamine afforded new polysubstituted thiazolo[4,5-c]pyrazole, thiazolo[4,5-d]-pyrimidine, thiazolo[4,5-b]-pyridine, thiazolo[4,5-b][1,5]benzodiazepine, thiazolo[4,5-b][1,5]benzoxazepine, thiazolo[4′,5′:6,5]-pyrimido[1,2-b][1,2,4]triazole and thiazolo-[4′,5′:6,5]pyrimido[1,2-b]pyrazole derivatives in good yields. The structure of the new compounds were confirmed based on IR, ^{1}H-, ^{13}C-NMR, mass spectral, and elemental analysis.

Keywords 2,3-Dihydrothiazole-5-carboxaldehyde; fused thiazole derivatives

INTRODUCTION

Thiazole derivatives have attracted a great deal of interest owing to their antimicrobial activity,[1,2] they used as antiviral, antimycobacterial and showed antiproliferative.[2] However, some of its derivatives proved as agent against constipation,[3] as potent and selective human adenosine A_3 receptor antagonists,[4–6] as inhibitors of VEGF receptors I and II,[7] as vanilloid receptor I TRPVI antagonists.[8] Also, some new thiazole derivatives have been found to possess anti-inflammatory and analgesic,[9–11] as potent and selective acetyl CoA carboxylase 2 inhibitors,[12] and have potential as possible treatments of Alzheimer's,[13] as noncovalent DNA-binding properties related to leinamycin.[14] Many thiazole derivatives have positive inotropic activity of the novel histamine H2-receptor agonist, amthamine, on the human

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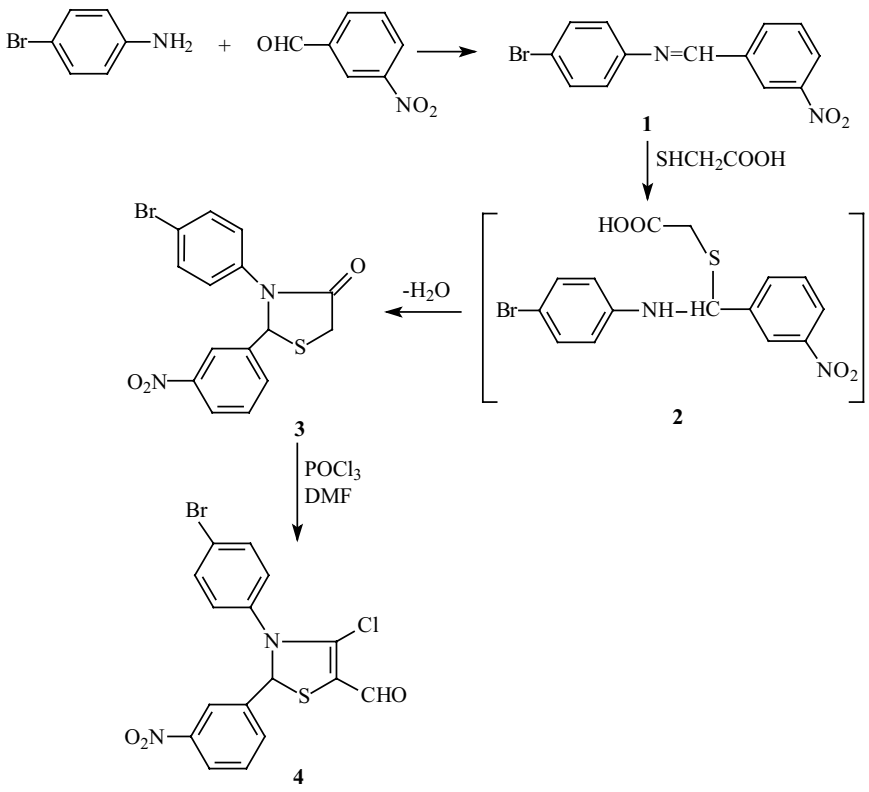
heart in vitro,[15] as antitumor agents,[16] as potent thrombin inhibitors,[17] against thrombocytopenia.[18] Moreover, thiazole derivatives well known for their biological properties, antifungal activities[19] and insecticidal activities.[20] On the other hand, fused thiazole heterocyclic compounds play an essential role in several biological processes and have considerable chemical importance. In particular, thiazolopyridines were found as histamine H_3-antagonists,[21] as inotropic activities.[22] Furthermore, thiazolopyrimidines can be found in a broad variety of pharmacological properties,[23] CXCR2 receptor antagonists,[24] as antagonists of $A_1$and A_2 adenosine receptors.[25] However, in continuation of our interest in the synthesis of fused heterocyclic derivatives,[26–30] which might have biological and/or medicinal effects, we report herein the utility of 4-chloro-2,3-dihydrothiazole-5-carboxaldehyde **4** for the synthesis of several new polysubstituted thiazole derivatives may found a medicinal uses.

RESULTS AND DISCUSSION

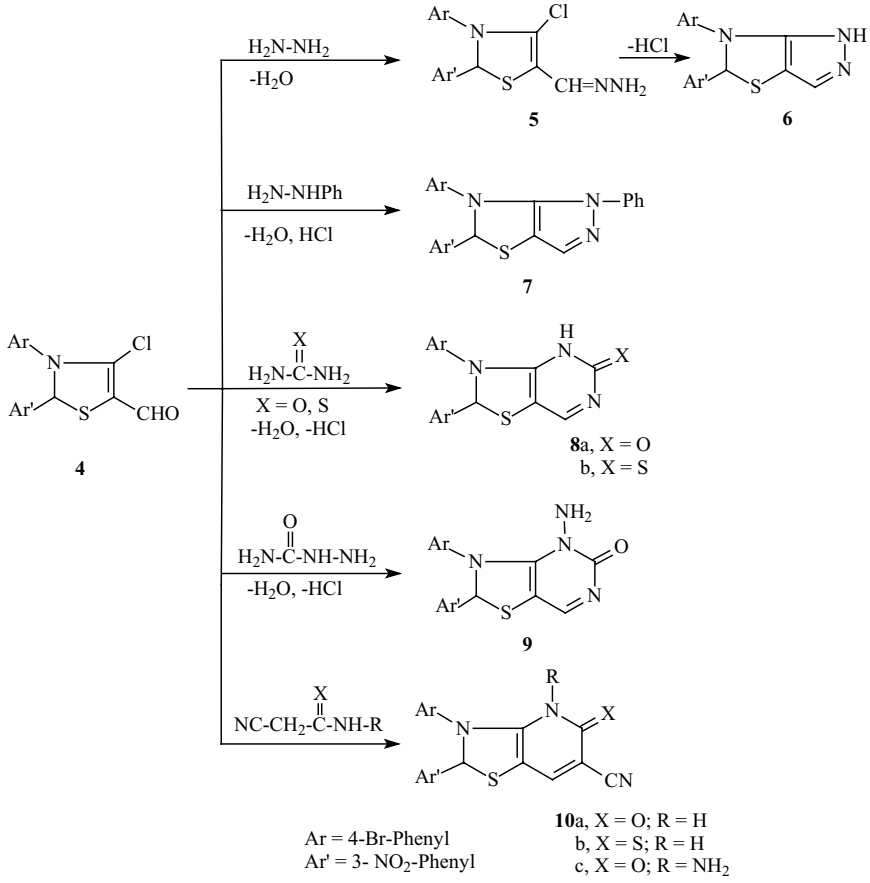
Thus, the reaction of 4-bromoaniline with 3-nitrobenzaldehyde in ethanolic piperidine solution at room temperature afforded the Schiff base **1** which reacted with thioglycolic acid in benzene at reflux yielded the thiazolidin-4-one derivative **3** through elimination of water from the intermediate **2**. The IR spectrum showed absorption bands at ν 1680 cm^{-1} due to the carbonyl of thiazolidinone. The MS of compound **3** showed *m/z* at 379 (M^+, 93), 298 (30), 252 (20), 236 (39%). The ^{1}H-NMR revealed singlet signal at δ 4.5 ppm assigned for methylene and a another singlet signal at 5.6 ppm for CH proton of thiazoldinone respectively, and the multiplets protons appeared atδ 7.1–7.9 ppm. Also, the ^{13}C-NMR showed signals at 30.2, 62.5, and 166.2 assigned for methylene, CH and carbonyl carbons of thiazolidinone.

However, the Vilsmeir formylation of thiazolidin-4-one **3** afforded 4-chloro-2,3-dihydrothiazolidine-5-carboxaldehyde **4** (Scheme 1). The IR spectrum showed bands at ν 1650 cm^{-1} due to CHO function. The MS of compound **4** showed *m/z* at 427 (M+2, 3), 425 (M^+, 10), 396 (30), 361 (20), 315 (39%). The ^{1}H-NMR revealed a new singlet signal at δ 9.7 ppm assigned for CHO proton and the disappearance of signal at 4.5 ppm. The ^{13}C-NMR indicates the disappearance of absorption at 30.2 and showed new signals at 135.1 and 153.5 ppm assigned for C—Cl and carbon of CHO group. The thiazole derivative **4** represents a versatile precursor for the synthesis of new fused thiazole derivatives.



SCHEME 1

Thus, products obtained from the reaction of the carboxaldehyde **4** with hydrazine hydrate depend on the reactions conditions. So, stirring of the reactants in ethanol at room temperature for 4 h yielded the corresponding Schiff base **5** in 85% yield. However, at reflux temperature in pyridine an cyclization reaction takes place to afford thiazolo[4,5-*c*]pyrazole **6** in 70% yield, (Scheme 2). It is noteworthy that, boiling of the isolated intermediate **5** in ethanol solution containing triethylamine yielded the compound **6** in 55% yield. The chemical structures of the compounds **5** and **6** based on spectral and elementals analysis. The IR spectrum of **5** showed absorption at band 3320 cm^{-1} due to NH_2 function with the disappearance of absorption of carbonyl function, whereas, the IR spectrum of compound **6** showed band at 3110 cm^{-1}due to the imino group. The MS of compound **5** showed *m/z* at 441 (M+2, 10), 439 (M^+, 30%) and the MS of compound **6** showed *m/z* at 404 (M+1, 20%). The ^{1}H-NMR of compound **5** showed signals at 5.1 and 8.6 ppm due to NH_2



SCHEME 2

and CH=N protons, respectively, whereas, the ^{1}H-NMR of **6** showed singlet signal at δ 5.6 assigned for the *H*-2-thiazole and new singlet signal at δ 6.8 assigned for *H*-6-pyrazole and lack of signal at 8.6 ppm. The ^{13}C-NMR of compound **5** showed new signals at 82.1 due to the carbon of –CH=NNH_2 which disappeared in the ^{13}C-NMR of compound **6**. Also, the reaction of compound **4** with phenyl hydrazine under the same reflux reaction conditions afforded directly the thiazolo[4,5-*c*]pyrazole derivatives **7**.

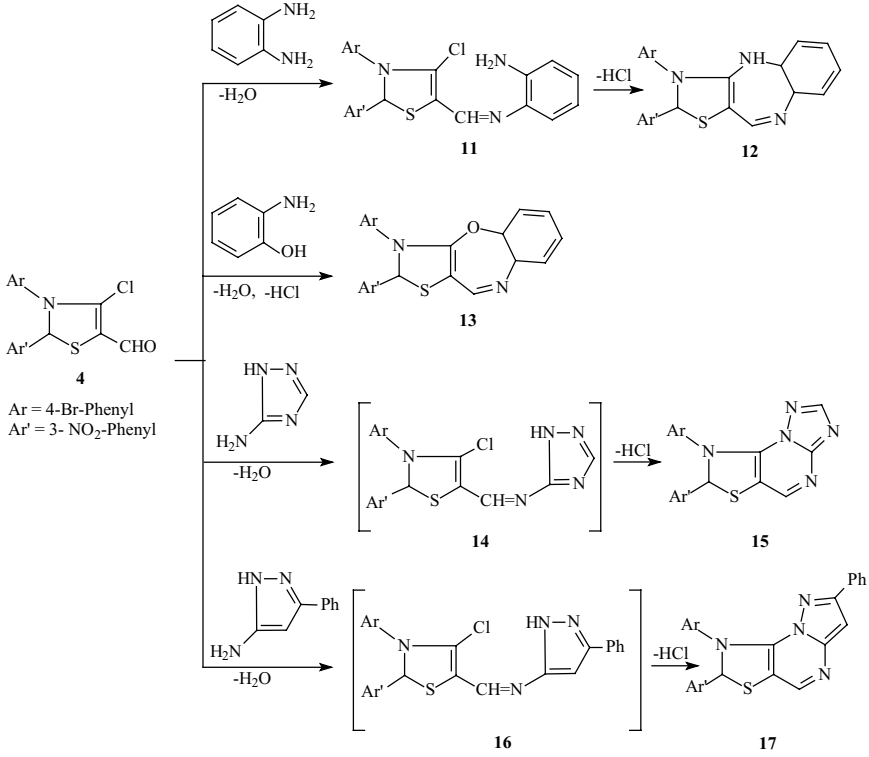
However, compound **4** represents a good synthon for thiazolopyrimidines, which found considerable interest in the medicinal and biological field.[31–33] Compound **4** reacted easily with urea and/or thiourea in ethanol solution containing triethylamine at reflux temperature

to afford thiazolo[4,5-*d*]pyrimidine derivatives **8a,b** via elimination of H_2O and hydrogen chloride (Scheme 2). The IR spectrum of **8a** showed the appearance of the characteristic absorption bands at 1690 and 3105 cm^{-1} assigned for carbonyl and imine functions, respectively. The MS of compound **8a** showed *m/z* at 431 (M^+, 15%), and its ^{13}C-NMR showed new signal at δ 152.4 ppm due to C=O.

Also, thiazolo[4,5-*d*]pyrimidine **9** obtained by a similar reaction of compound **4** with semicarbazide under the same reaction conditions. The chemical structures of the product based on spectral and elemental analysis, (Scheme 2). However, a new thiazolopyridines have been prepared via the reaction of compound **4** with cyanoacetamide, cyanothioacetamide and cyanoacetohydrazide in absolute ethanol in the presence of triethylamine at reflux temperature to yield thiazolo[4,5-*b*]pyridines **10** via elimination of water and hydrogen chloride, (Scheme 2). The IR spectrum of **10a** revealed absorption bands at 1695 (CO), 2210 (CN), 3115 (NH) functions. The MS of **10a** showed *m/z* at 455 (M^+, 10%). The ^{1}H-NMR of **10a** showed singlet signal at δ 5.6 ppm and multiplets at δ 7.1–7.9 ppm. Also, the ^{13}C-NMR showed signal at 114.2 ppm for CN and at 158.4 ppm for C=O.

However, the carboxaldehyde **4** reacted further with 2-phenylenediamine in ethanol solution containing triethylamine as catalyst, and at reflux temperature afforded a product. The IR spectrum of the product showed absorption band at 3340 cm^{-1} assigned for amino function and revealed the lack of CHO absorption. The ^{1}H-NMR showed a new signal at δ 8.2 ppm for 1H. The mass measurement showed *m/z* at 518 (M+2, 5), 516 (M^+, 15%), which indicates that the product is an open compound containing the chlorine atom. When the reaction conducted in pyridine as a solvent at reflux the mass spectrum of the product showed *m/z* at 479 indicating that the Schiff's base **11** considered as an isolated intermediate for the thiazolodiazepine derivative **12**. The IR spectrum of compound **12** showed the absence of the absorption band of amino function at 3340 cm^{-1} and appearance of band at 3110 cm^{-1}due to imino group. The ^{1}H-NMR of **12** showed the disappearance of the signal at δ 8.2 and showed singlet signal at δ 5.2 ppm for *H*-2-thiazole and multiplets at δ 7.0–7.8 ppm. Also, the isolated intermediate **11** was successfully transformed into **12** via boiling in pyridine. On the other hand, in the case of 2-aminophenol the thiazolo-1,5-benzoxapine derivative, **13** was obtained directly using ethanol / triethylamine solution.

Finally, the reactivity of carboxaldehyde **4** towards some of amino heterocyclic nucleophiles was also investigated. Thus, compounds **4** reacted with each of 5-amino-1*H*-1,2,4-triazole and 5-amino-3-phenyl-1*H*-pyrazole in ethanolic triethylamine solution at reflux



SCHEME 3

temperature to give thiazolo[4′,5′:6,5]pyrimido[1,2-*b*]triazole **15** and thiazolo[4′,5′:6,5]pyrimido[1,2-*b*]pyrazole **17**, respectively via elimination of water and hydrogen chloride (Scheme 3). The structure of **15** and **17** were established based on spectral and elemental analysis.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra (potassium bromide, ν in cm^{-1}) were recorded on a Pye-Unicam SP-1100 Spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra (deuterodimethyl sulfoxide, δ in ppm) were run on a Varian EM-390 Spectrometer using Tetramethylsilane as internal standard. Mass spectra were recorded on a Varian MAT 311 A spectrometer, and the elemental analysis was determined at the Micro-analytical Center, Cairo University, Egypt.

3-(4-Bromophenyl)-2-(3-nitrophenyl)thiazolidin-4-one 3

A solution of **1** (0.6 g, 2 mmol), thioglycolic acid (0.25 g, 2 mmol), in 30 ml of dry benzene was warmed at reflux for 2 h. The solid product so formed during reflux was collected by filtration, dried and crystallized from ethanol. M.p.: 160°C, Yield: 90%. IR: ν 1680 (CO) cm^{-1}; ^1H NMR: δ 4.5 (*s*, 2H, CH_2-thiaz.), 5.6 (*s*, H, CH-thiaz.), 7.1–7.9 (*m*, 8H, Ar-H); ^{13}C NMR: 166.2 (C=O), 123.6–135.5 (C-Phenyl), 62.5(C-2), 30.2 (C-5); MS (70 eV) *m/z* (%): 379 (M^+, 93). Anal. calcd. For $C_{15}H_{11}BrN_2O_3S$ (379.23): C, 47.51; H, 2.92; N, 7.39. Found: C, 47.59; H, 2.82; N, 7.49.

3-(4-Bromophenyl)-4-chloro-2,3-dihydro-2-(3-nitrophenyl)thiazole-5-carboxaldehyde 4

A solution of thiazolidin-4-one **3** (0.2 mol) in DMF (50 ml) was cooled to 0°C in an ice bath, then phosphoryl chloride (0.6 mol) was added dropwise at such a rate as to maintain the temperature between 10–20°C. The reaction mixture was then heated on water bath for an additional three hours after completion of addition. The mixture was then poured onto ice- water, and the resulting mixture allowed to stand overnight in a refrigerator. The solid product thus obtained was filtered, washed well with water, dried to give compound **4** as brown powder, and crystallized from methanol.

M.p.: 140°C, Yield: 46%. IR: ν 1650 (CO) cm^{-1}; ^1H NMR: δ 5.6 (*s*, H, CH), 9.7 (*s*, H, CHO), 7.1–7.9 (*m*, 8H, Ar-H); ^{13}C NMR: 153.5 (C=O), 153.5 (C-5), 135.1 (C-4), 123.6–134.5 (C-Phenyl), 62.5 (C-2); MS (70 eV) *m/z* (%): 427 (M+2, 3), 425 (M^+, 10). Anal. calcd. For $C_{16}H_{10}BrClN_2O_3S$ (425.68): C, 45.15; H, 2.37; N, 6.59. Found: C, 45.19; H, 2.47; N, 6.45.

3-(4-Bromophenyl)-4-chloro-2,3-dihydro-5-methyene hydrazine-2-(3-nitrophenyl) thiazole 5

A solution of carboxaldehyde **4** (0.4 g, 1 mmol), hydrazine hydrate (0.3 ml, excess) in 30 ml of dry ethanol was stirred at room temperature for 4 h and the solid formed was collected by filtration, washed well with 3 ml of methanol and crystallized from ethanol to give **5**.

M.p.: 150°C, Yield: 85%. IR: ν 3320 (NH_2) cm^{-1}; ^1H NMR: δ 5.1 (*s*, 2H, NH_2), 5.5 (*s*, H, CH thiaz.), 7.1–7.9 (*m*, 8H, Ar-H), 8.6 (*s*, H, CH=N); ^{13}C NMR: 134.7 (C-4), 133.5 (C-5), 123.6–132.5 (C-Phenyl), 82.1 (CH=N-), 62.2 (C-2); MS (70 eV) *m/z* (%): 441 (M+2, 10), 439 (M^+, 30). Anal. calcd. For $C_{16}H_{12}BrClN_4O_2S$ (439.72): C, 43.70; H, 2.75; N, 12.74. Found: C, 43.99; H, 2.98; N, 12.64.

3-(4-Bromophenyl)-2,3-dihydro-2-(3-nitrophenyl)-4H-thiazolo[4,5-*c*]pyrazole 6

A solution of carboxaldehyde **4** (0.4 g, 1 mmol), hydrazine hydrate (0.3 ml, excess) in 20 ml of pyridine was warmed at reflux for 4 h. The solvent was evaporated under vacuum and the residue was poured on ice / water acidified by hydrochloric acid (1 ml HCl, 20 ml H_2O). The solid product collected by filtration and washed well with water to give compound **6**.

M.p.: 165°C, Yield: 70%. IR: ν 3110 (NH) cm^{-1}; ^1H NMR: δ 5.6 (*s*, H, CH-thiaz.), 6.8 (*s*, H, CH-pyraz.), 7.1–7.9 (*m*, 9H, Ar-H + NH); ^{13}C NMR: 123.6–133.7 (C-Phenyl), 129.5 (C-6a), 128.7 (C-6), 127.6 (C-3a), 62.9 (C-2); MS (70 eV) *m/z* (%): 404 (M+1, 20). Anal. calcd. For $C_{16}H_{11}BrN_4O_2S$ (403.26): C, 47.66; H, 2.75; N, 13.89. Found: C, 47.70; H, 2.98; N, 13.77.

3-(4-Bromophenyl)-2,3-dihydro-2-(3-nitrophenyl)-4-phenyl-thiazolo[4,5-*c*]pyrazole 7

A solution of carboxaldehyde **4** (0.4 g, 1 mmol), phenyl hydrazine (0.15 g, 1 mmol), and 0.2 ml of triethylamine in 30 ml of dry ethanol was refluxed for 5 h and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from a mixture of methanol and water (3:1) to give **7**.

M.p.: 155°C, Yield: 60%. ^1H NMR: δ 5.7 (*s*, H, CH-thiaz.), 6.8 (*s*, H, CH-pyraz.), 7.3–7.8 (*m*, 8H, Ar-H); MS (70 eV) *m/z* (%): 480 (M+1, 25). Anal. calcd. For $C_{22}H_{15}BrN_4O_2S$ (479.36): C, 55.12; H, 3.15; N, 11.69. Found: C, 55.21; H, 3.29; N, 11.81.

General Procedure to Prepare Compounds 8a,b

To ethanol solution (30 ml) of carboxaldehyde **4** (0.8 g, 2 mmol), an equimolar amount of urea (0.12 g, 2 mmol) was added and the mixture was refluxed in the presence of 0.2 ml of triethylamine for 6 h. The reaction mixture was evaporated under vacuum and the residue poured into acidified cold water (1 ml HCl, 20 ml H_2O). The solid formed was collected by filtration, washed well with 100 ml of cold water, and crystallized from a mixture of methanol and water (3:1) to give **8a**. Analogously, compound **4** reacted with thiourea to give **8b**.

3-(4-Bromophenyl)-2,3-dihydro-2-(3-nitrophenyl) -thiazolo[4,5-d]pyrimidine-5(4H)-one 8a

M.p.: 180°C, Yield: 50%. IR: ν 1690 (CO), 3105 (NH) cm^{-1}; ^1H NMR: δ 5.6 (*s*, H, CH-thiaz.), 7.2–7.9 (*m*, 10H, Ar-H + NH); ^{13}C NMR: 152.4 (CO),

123.6–132.7 (C-Phenyl), 129.4 (C-7a), 128.4 (C-7), 127.5 (C-3a), 62.7 (C-2); MS (70 eV) *m/z* (%): 431 (M^+, 15). Anal. calcd. For $C_{17}H_{11}BrN_4O_3S$ (431.27): C, 47.35; H, 2.57; N, 12.99. Found: C, 47.51; H, 2.76; N, 12.80.

3-(4-Bromophenyl)-2,3-dihydro-2-(3-nitrophenyl) -thiazolo[4,5-d]pyrimidine-5(4H)-thione 8b

M.p.: 165°C, Yield: 56%. IR: ν 3100 (NH) cm^{-1}; ^1H NMR: δ 5.9 (*s*, H, CH-thiaz.), 7.1–7.9 (*m*, 10H, Ar-H + NH); MS (70 eV) *m/z* (%): 447 (M^+, 10). Anal. calcd. For $C_{17}H_{11}BrN_4O_2S_2$ (447.34): C, 45.64; H, 2.48; N, 12.52. Found: C, 45.90; H, 2.54; N, 12.61.

4-Amino-3-(4-bromophenyl)-2,3-dihydro-2-(3-nitrophenyl)-thiazolo[4,5-d]pyrimidine-5-one 9

Equimolar amounts of carboxaldehyde **4** (0.8 g, 2 mmol) and semicarbazide (0.15 g, 2 mmol) were refluxed in ethanol containing 0.2 ml of triethylamine for 7 h. The ethanol solution was evaporated under vacuum and the resulting emulsion was triturated with 5 ml of methanol and then poured into acidified cold water (1 ml HCl, 20 ml H_2O). The solid product that formed was collected by filtration, washed well with 100 ml of cold water, and crystallized from a mixture of ethanol and water (3:1) to give **9**.

M.p.: 185°C, Yield: 50%. IR: ν 1698 (CO), 3310 (NH_2) cm^{-1}; ^1H NMR: δ 5.7 (*s*, H, CH-thiaz.), 7.1–7.9 (*m*, 11H, Ar-H + NH_2); MS (70 eV) *m/z* (%): 447 (M+1, 20). Anal. calcd. For $C_{17}H_{12}BrN_5O_3S$ (446.29): C, 45.75; H, 2.71; N, 15.69. Found: C, 45.91; H, 2.89; N, 15.81.

General Procedure to Prepare Compounds 10a–c

A solution of carboxaldehyde **4** (0.8 g, 2 mmol), cyanoacetamide (0.16 g, 2 mmol), and 0.2 ml of triethylamine in 30 ml of dry ethanol was refluxed for 5 h and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from a mixture of methanol and water (3:1) to give **10a**. Analogously, compound **4** reacted with equimolar amounts of cyanothioacetamide and cyanoacetohydrazide to give **10b,c** derivatives, respectively.

3-(4-Bromophenyl)-2,3,4,5-tetrahydro-2-(3-nitrophenyl)-5-oxo-thiazolo[4,5-b]pyridine-6-carbonitrile 10a

M.p.: 170°C, Yield: 59%. IR: ν 1695(CO), 2210 (CN), 3115 (NH)) cm^{-1}; ^1H NMR: δ 5.6 (*s*, H, CH- thiaz.), 7.1–7.9 (*m*, 10H, Ar-H +NH); ^{13}C NMR: 158.4 (CO), 130.5 (C-6), 123.6–132.7 (C-Phenyl), 129.7 (C-7a),

128.7 (C-7), 126.4 (C-3a), 114.2 (CN), 62.5 (C-2); MS (70 eV) *m/z* (%): 455 (M^+, 10). Anal. calcd. For $C_{19}H_{11}BrN_4O_3S$ (455.30): C, 50.12; H, 2.43; N, 12.31. Found: C, 50.33; H, 2.57; N, 12.49.

3-(4-Bromophenyl)-2,3,4,5-tetrahydro-2-(3-nitrophenyl)-5-thioxothiazolo[4,5-b]pyridine-6-carbonitrile 10b

M.p.: 190°C, Yield: 50%. IR: ν 2225 (CN), 3123 (NH)) cm^{-1}; ^1H NMR: δ 5.7 (*s*, H, CH-thiaz.), 7.1–7.9 (*m*, 10H, Ar-H +NH); MS (70 eV) *m/z* (%): 471 (M^+, 10). Anal. calcd. For $C_{19}H_{11}BrN_4O_2S_2$(471.36): C, 48.42; H, 2.35; N, 11.89. Found: C, 48.58; H, 2.61; N, 11.75.

4-Amino-3-(4-bromophenyl)-2,3,5-tetrahydro-2-(3-nitrophenyl)-5-oxothiazolo[4,5-b]pyridine-6-carbonitrile 10c

M.p.: 195°C, Yield: 56%. IR: ν 1694 (CO), 2226 (CN), 3327 (NH_2)) cm^{-1}; ^1H NMR: δ 5.7 (*s*, H, CH- thiaz.), 7.1–7.9 (*m*, 11H, Ar-H + NH_2); MS (70 eV) *m/z* (%): 472 (M+2, 30). Anal. calcd. For $C_{19}H_{12}BrN_5O_3S$(470.31): C, 48.52; H, 2.57; N, 14.89. Found: C, 48.77; H, 2.75; N, 14.76.

3-(4-Bromophenyl)-4-chloro-2-(3-nitrophenyl)-5-methylene-*N*-2-(phenylenediamine) thiazole 11

A solution of carboxaldehyde **4** (0.4 g, 1 mmol), 2-phenylenediamine (0.12 g, 1 mmol), and 0.2 ml of triethylamine in 30 ml of dry ethanol was warmed at reflux for 5 h and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from a mixture of methanol and water (3:1) to give **11**.

M.p.: 200°C, Yield: 60%. IR: ν 3340 (NH_2) cm^{-1}; ^1H NMR: δ 5.6 (*s*, H, CH-thiaz.), 7.1–7.8 (*m*, 14H, Ar-H + NH_2), 8.2 (*s*, H, CH=N);^{13}C NMR: 135.4 (C-4), 123.6–132.5 (C-Phenyl), 129.1 (C-5),75.6 (CH=N-), 62.5 (C-2); MS (70 eV) *m/z* (%): 518 (M+2, 5%), 516 (M^+, 15%). Anal. calcd. For $C_{22}H_{16}ClBrN_4O_2S$(515.82): C, 51.22; H, 3.13; N, 10.86. Found: C, 51.35; H, 3.25; N, 10.94.

3-(4-Bromophenyl)-2,3,4-trihydro-2-(3-nitrophenyl)-thiazolo[4,5-*b*][1,5]benzodiazepine 12

A solution of carboxaldehyde **4** (0.4 g, 1 mmol), 2-phenylenediamine (0.12 g, 1 mmol), in 20 ml of pyridine was warmed at reflux for 4 h The solvent was evaporated under vacuum and the residue was poured on ice/water acidified by hydrochloric acid (1 ml HCl, 20 ml H_2O). The

solid product collected by filtration and washed well with water to give compound **12**.

M.p.: 210°C, Yield: 56%. IR: ν 3110 (NH) cm^{-1}; ^1H NMR: δ 5.2 (*s*, H, CH-thiaz.), 7.0–7.8 (*m*, 14H, Ar-H + NH);^{13}C NMR: 123.6–132.7 (C-Phenyl), 129.4 (C-7a), 128.4 (C-7), 127.6 (C-10), 126.5 (C-4a), 126.1 (C-3a), 62.7 (C-2); MS (70 eV) *m/z* (%): 479 (M^+, 10). Anal. calcd. For $C_{22}H_{15}BrN_4O_2S$(479.36): C, 55.12; H, 3.15; N, 11.69. Found: C, 55.28; H, 3.39; N, 11.75.

3-(4-Bromophenyl)-2,4-dihydro-2-(3-nitrophenyl)-thiazolo[4,5-*b*][1,5]benzoxazepine 13

A solution of carboxaldehyde **4** (0.4 g, 1 mmol), 2-aminophenol (0.11 g, 1 mmol), and 0.2 ml of triethylamine in 30 ml of dry ethanol was warmed at reflux for five hours and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from a mixture of methanol and water (3:1) to give **13**.

M.p.: 205°C, Yield: 49%. ^1H NMR: δ 5.4 (*s*, H, CH-thiaz.), 7.1–7.9 (*m*, 13H, Ar-H); MS (70 eV) *m/z* (%): 480 (M^+, 10). Anal. calcd. For $C_{22}H_{14}BrN_3O_3S$(480.35): C, 55.01; H, 2.94; N, 8.75. Found: C, 55.22; H, 2.88; N, 8.94.

General Procedure to Prepare Compounds 15 and 17

A solution of carboxaldehyde **4** (0.8 g, 2 mmol), 5-amino-1,2,4-triazole (0.16 g, 2 mmol), and 0.2 ml of triethylamine in 30 ml of dry ethanol was warmed at reflux for 7 h and concentrated under vacuum. The solid formed after addition of cold diluted HCl (1 ml, 20 ml H_2O) was collected by filtration, washed well with 100 ml of cold water and crystallized from a mixture of methanol and water (3:1) to give compound **15**. Analogously, compound **4** reacted with equimolar amount of 3-aminopyrazole to give compound **17**.

3-(4-Bromophenyl)-2,3-dihydro-2-(3-nitrophenyl)-thiazolo[4′,5′:6,5]pyrimido[1,2-*b*][1,2,4]triazole 15

M.p.: 195°C, Yield: 56%. ^1H NMR: δ 5.4 (*s*, H, CH-thiaz.), 7.1–7.8 (*m*, 10H, Ar-H); ^{13}C NMR: 123.6–132.5 (C-Phenyl), 132.4 (C-6), 130.1 (C-9a), 129.6 (C-3a), 128.8 (C-9), 62.7 (C-2); MS (70 eV) *m/z* (%): 455 (M^+, 7). Anal. calcd. For $C_{18}H_{11}BrN_6O_2S$ (455.30): C, 47.48; H, 2.44; N, 18.46. Found: C, 47.56; H, 2.63; N, 18.74.

3-(4-Bromophenyl)-6-phenyl-2,3-dihydro-2-(3-nitrophenyl)-thiazolo[4′,5′:6,5]pyrimido[1,2-b]pyrazole **17**

M.p.: 150°C, Yield: 56%. ^{1}H NMR: δ 5.5 (*s*, H, CH-thiaz.), 7.1–7.9 (*m*, 15H, Ar-H); MS (70 eV) *m/z* (%): 531 (M+1, 10). Anal. calcd. For $C_{25}H_{16}BrN_5O_2S$ (530.41): C, 56.61; H, 3.04; N,13.21. Found: C, 56.74; H, 3.14; N,13.77.

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