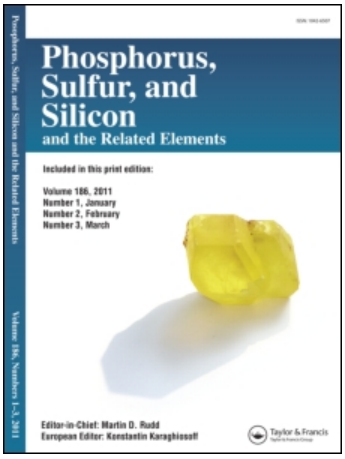

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Nitriles in Organic Synthesis: Synthesis of New Benzothiazole Derivatives of Biological Interest

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NITRILES IN ORGANIC SYNTHESIS: SYNTHESIS OF NEW BENZOTHIAZOLE DERIVATIVES OF BIOLOGICAL INTEREST

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Cyanobenzothiazole (1) was utilized for the synthesis of several new fused and 2-heterylbenzothiazole derivatives such as pyrimido, pyridino, quinolino, pyrazolopyranyl, pyrimidinopyranyl, and cyclohexanopyranyl benzothiazole derivatives.

Keywords Benzothiazole; 2-cyanomethylbenzothiazole; formaldehyde; pyrazole

INTRODUCTION

Recently there have been broad developments in investigations of both the synthesis and the study of the chemical properties of benzothiazole derivatives, which have valuable pharmacological activities.[1–3] Several lines of evidence support the hypothesis that 2-cyanomethylbenzothiazole (1) has resulted in their synthesis and chemistry. For the past decade, we have been exploring the synthetic potential, scope, and limitations of 2-cyanomethylbenzothiazole and other activated nitriles in heterocyclic synthesis.[4–7] Several new approaches for the synthesis of five-membered and six-membered rings and their fused heterocyclic derivatives have been developed during our research that has resulted in this article.

2-Cyanomethylbenzothiazole (**1**), in the presence of various reagents, undergoes different types of reactions to yield other heterocyclic compounds of biological and industrial interest.

These advances warrant a review of the chemistry and biological properties of 2-cyanomethylbenzothiazole and highlight its potential in developing synthetic uses.[8]

RESULTS AND DISCUSSION

In continuation of our interest in heterocyclic synthesis of compounds with potential pharmacological value, we decided to study the synthetic potentiality of

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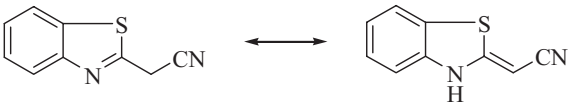
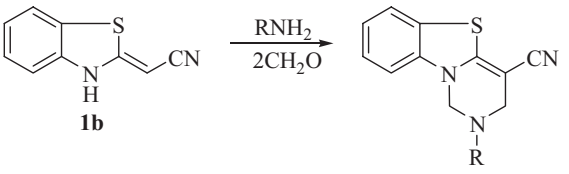
2-cyanomethylbenzothiazole (**1**) towards some reagents as a convenient route to some condensed and substituted benzothiazoles.

The reactivity of 2-cyanomethylbenzothiazole (**1a**) can be attributed to the contribution of a resonance structure (**1b**), which is analogous to enamines (Scheme 1). It has been reported that enamines react with primary amines and 2 mol of formaldehyde to yield tetrahydropyrimidines.[9–11] Thus, it was of interest to study the behavior of 2-cyanomethylbenzothiazole (**1**) towards a double Mannich reaction as a route to condensed pyrimidine systems (Scheme 2).



1a **1b**

Scheme 1



1b **2a-d**

2	R
a	-CH_2-C_6H_5
b	-CH_2-$(CH_2)_2CH_3$
c	-$CH(CH_3)_2$
d	-cyclohexyl

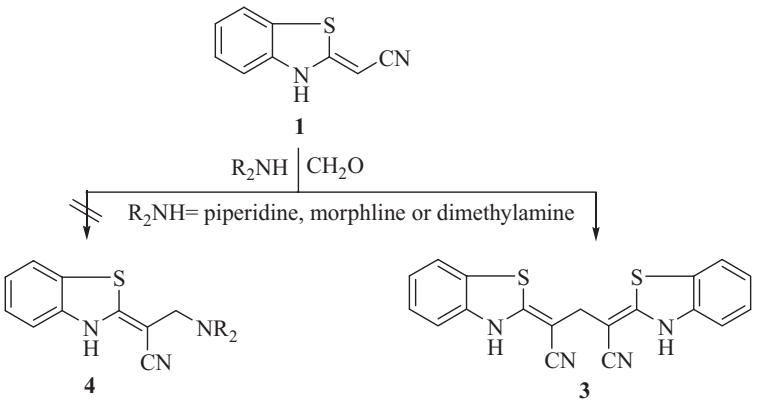
Scheme 2

Therefore, when 2-cyanomethylbenzothiazole (**1**) was treated with primary amines such as benzylamine, *n*-butylamine, isopropylamine, or cyclohexylamine and formalin in a molar ratio of 1:1:2, the pyrimidobenzothiazole derivatives (**2a–d**), respectively, were obtained. The analytical and spectral data are consistent with the proposed structures of compounds (**2a–d**) (see the Experimental section).

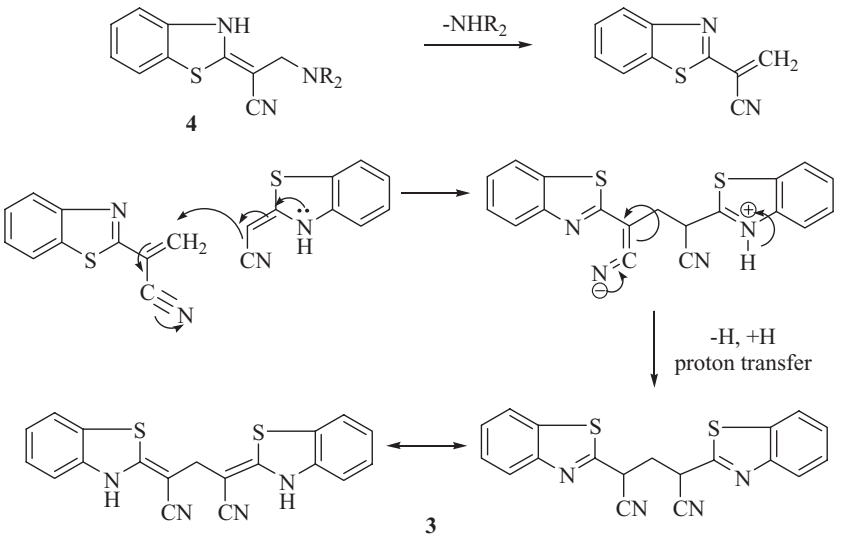
The IR spectra of these products showed stretching frequencies at 2194–2155 cm^{-1} for CN function group. The mass spectra of (**2a–d**) showed the molecular ion peak at *m/z* 305 (M^+, 65%), 271 (M^+ as base peak), 257 (M^+, 43%) and 297 (M^+, 9.7%), respectively. In addition, the ^1H NMR spectrum of (**2a**) exhibited signals at δ 3.0 (d, J = 12.3 Hz, 2H, CH_2—N), δ 3.69 (d, J = 11.5 Hz, 2H, N—CH_2—N), δ 3.90 (s, 2H, CH_2—Ph) and a complex pattern at δ 7.25–8.01 (9H, aromatic).

Alternatively, treatment of (**1**) with formalin and secondary amines, such as piperidine, morphline, or dimethylamine in a molar ratio of 1:1:1 under Mannich reaction conditions afforded the methylene bis-compound (**3**) rather than the expected compound (**4**). The structure of 1,3-dicyano-1,3-di[benzothiazol-2-yl]propane (**3**) was determined by analytical and spectral data (Scheme 3).

The formation of (**3**) could be rationalized through a mechanism that involves the formation of (**4**) as an intermediate followed by deamination and attack on the enamine (**1**) (see Scheme 4).



Scheme 3

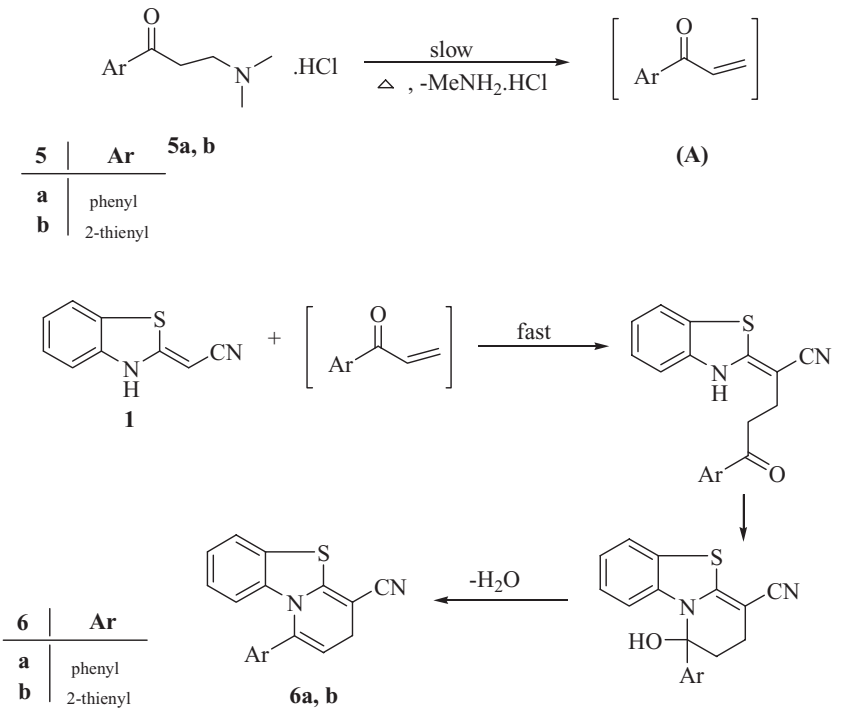


Scheme 4

The IR spectrum of compound (**3**) showed absorption bands around the region 2220 cm^{-1} attributable to the cyano groups. The ^1H NMR spectrum of the reaction product revealed the CH_2 protons and CH protons as multiplet at δ 3.4–3.8 ppm due to vicinal and geminal coupling and a multiplet at δ 7.1–8.1 ppm due to aromatic protons.

The structure of (**3**) was further confirmed by an alternative synthesis. Thus, treatment of (**1**) with formalin in a molar ratio of 2:1 in refluxing ethanol yielded a product identical in all respects (mp, mixed mp, IR, and ^1H NMR) with (**3**).[7]

It has been reported that 6-amino-1,3-dimethyluracil reacts with an equimolar amount of ketonic Mannich base hydrochloride (**5**) to give the pyrido[2,3-d]pyrimidin-2,4-diones.[12] Also, Troschhutz et al.[13] found that the reaction between the nitroketeneaminal and ketonic Mannich bases hydrochloride (**5**) gave the pyrido[1,2-a]pyrimidines. Thus, it was of interest to study the reaction of 2-cyanomethylbenzothiazole (**1**) with ketonic Mannich bases (**5**) as a route to the pyrido[2,1-b][1,3]benzothiazole ring system.



Scheme 5

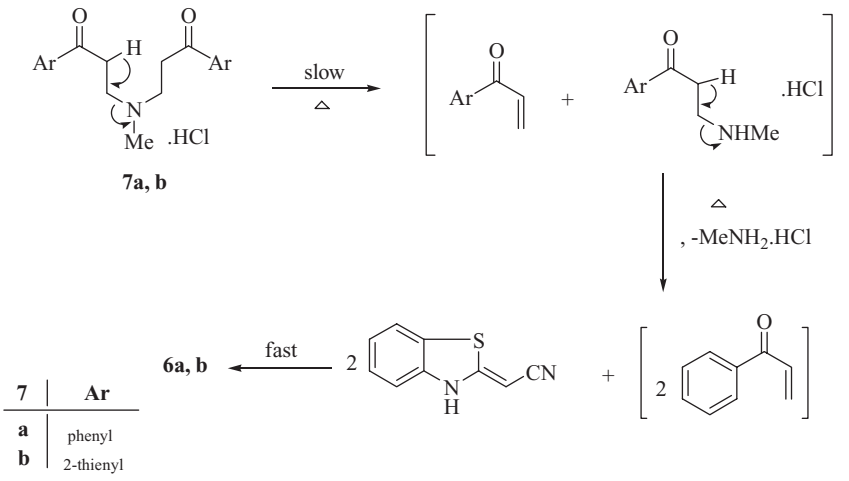
We found that compound (**1**) reacted with the ketobases hydrochloride (**5a**,**b**) in a molar ratio of 1:1 in ethanol in the presence of a catalytic amount of acetic acid to afford 4-cyano-1-aryl-3*H*-pyrido[2,1-b][1,3]benzothiazoles (**6a**,**b**) (see Scheme 5).

The formation of (**6a**,**b**) can be explained by a mechanism that involves an initial deamination of the keto-bases hydrochloride (**5a**,**b**) to give the aryl vinyl ketone (**A**) as an intermediate. Then the active CH of (**1**) was added to the vinyl double bond, followed by cyclization and loss of a water molecule to give the product (**6a**,**b**).

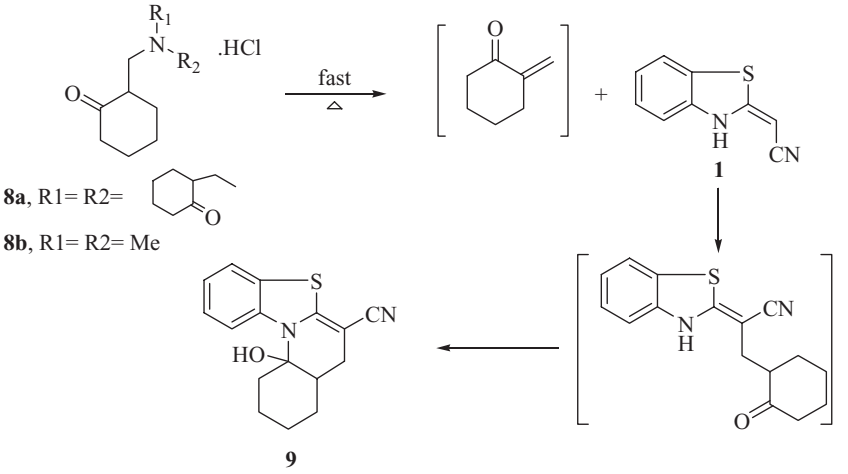
In addition, the products (**6a**,**b**) were also obtained when (**1**) was subjected to react with the diketo-bases hydrochloride (**7a**,**b**) in a molar ratio of 2:1 under the same reaction conditions (see Scheme 6). In this case, the aryl vinyl ketone is formed through two successive deamination reactions of the diketo-base (**7**). In this reaction, it is clear that the substitution pattern at C-1 of the annelated pyridine ring is determined by the structure of the bis-electrophile (aryl vinyl ketone). The ^{1}H NMR of (**6b**) showed a doublet at δ 3.51 (J = 6.6 Hz, 2H, C-3), a triplet at δ 3.69 (1H, C-2), a complex pattern at δ 7.53–7.68 (4H, phenyl), and a multiplet at δ 7.71–8.04 (3H, thienyl). The mass spectrum of (**6a**) showed the molecular ion peak at *m/z* 289 (M^++1, 32%).

As an interesting extension of the present research, the synthesis of quinolino[2,1-b]benzothiazole (**9**) has been achieved by treating the cyclic keto-base hydrochloride (**8b**) or the diketo-base hydrochloride (**8a**) with (**1**) (see Scheme 7).

All attempts to dehydrate the hydroxyquinolino[2,1-b]benzothiazole (**9**) to (**10**) or (**11**) under different reaction conditions such as using glacial acetic, concentrated hydrochloric or *p*-toluensulfonic acid were unsuccessful (see Figure 1).



Scheme 6



Scheme 7

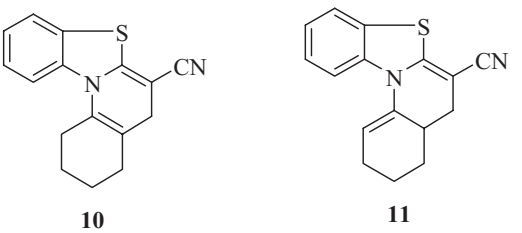
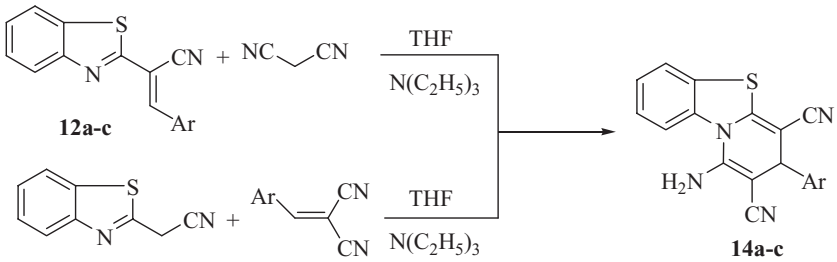


Figure 1

The difficulty of the dehydration of (**9**) may be due to the instability of the bridged intermediate carbocation during the E1 process. The IR spectrum of (**9**) showed strong absorption bands at 3452 (OH) and 2179 (CN) cm^{-1}. Its mass spectrum exhibited a molecular ion peak at *m/z* 284 (M^+, 57.5%), 283 ($M^+ - 1$, 100% as base peak) and 282 ($M^+ - 2$, 37.5%).

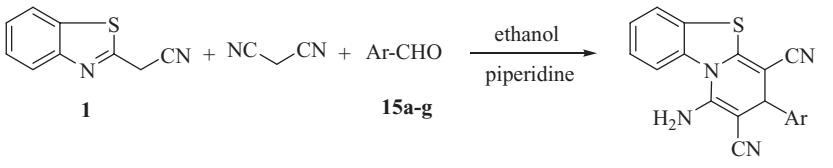
In addition, it has been reported[14] that 1-amino-2,4-dicyano-3-aryl-3*H*-pyrido[2,1-b]benzothiazoles (**14a–c**) were synthesized in (50–70%) yield either by condensation of 2-arylidenecyanomethylbenzothiazoles (**12a–c**) with malononitrile in THF/$N(C_2H_5)_3$, or by condensation of 2-cyanomethylbenzothiazole (**1**) with arylidenemalononitrile (**13a–c**) under the same reaction conditions (see Scheme 8). We report in this article the synthesis of some new 1-amino-2,4-dicyano-3-aryl-3*H*-pyrido[2,1-b]benzothiazoles (**14a–g**) in excellent yield by a convenient one-pot method from the laboratory available reagents. Thus, condensation of benzaldehyde derivatives (**15a–g**), malononitrile, and (**1**) in a molar ratio of 1:1:1 in ethanolic piperidine afforded the pyrido[2,1-b]benzothiazole (**14a–g**) in excellent yield (see Scheme 9).



12a-c **1** **13a-c** **14a-c**

14	Ar
a	-C_6H_5
b	4-OCH_3-C_6H_4
c	4-Cl-C_6H_4

Scheme 8

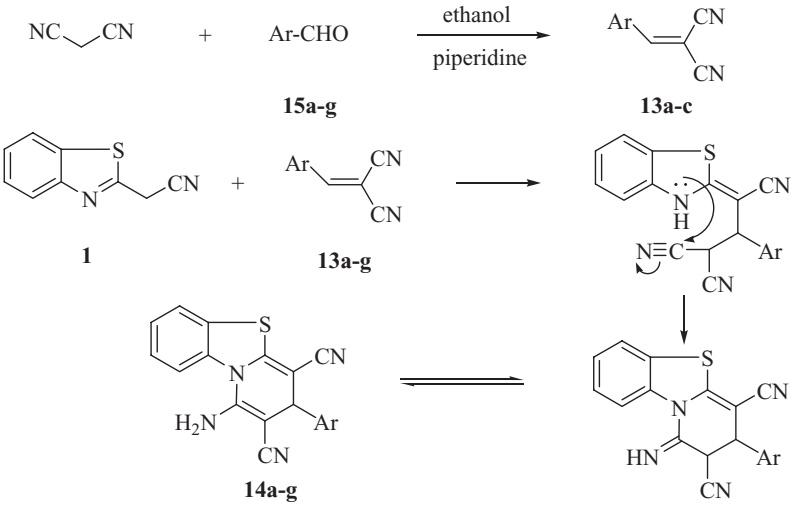


1 **15a-g** **14a-g**

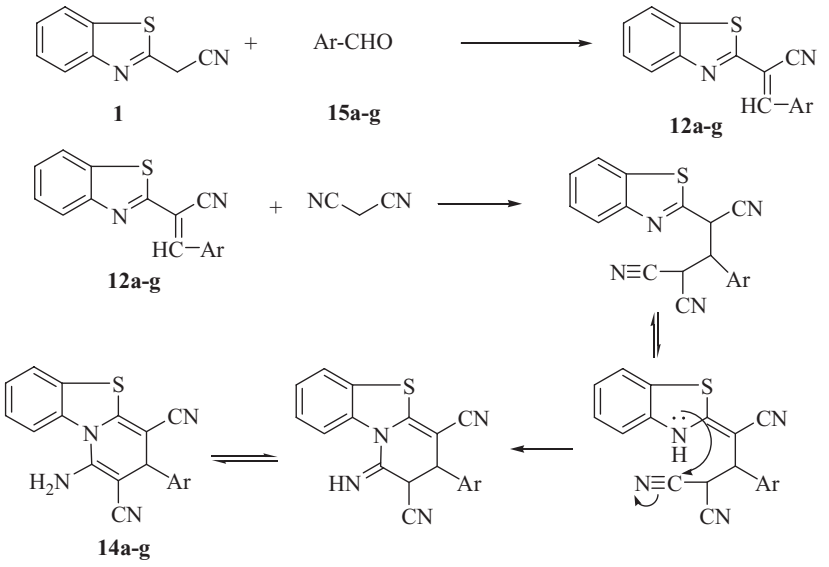
14, 15	Ar
a	-C_6H_5
b	4-OCH_3-C_6H_4
c	4-Cl-C_6H_4
d	4-Br-C_6H_4
e	4-NO_2-C_6H_4
f	4-$N(CH_3)_2$-C_6H_4
g	3,4-O-CH_2O-C_6H_3

Scheme 9

Formation of (**14**) is assumed to proceed by two parallel mechanisms, and that explains the excellence of the yield. The first mechanism involves initial condensation of aldehyde with malononitrile, affording the formation of arylidenemalononitriles (**13**), followed by Michael addition of 2-cyanomethyl-1,3-benzothiazole (**1**) to the ylidenic bond in (**13**), forming an acyclic intermediate, which, cyclized by nucleophilic attack of the NH on the cyanocarbon, was followed by tautomerization to the final product (**14**) (see Scheme 10). The second mechanism involves initial condensation of aromatic aldehydes to 2-cyanomethylbenzothiazole, affording the 2-arylidenecyanomethylbenzothiazole (**12**), followed by Michael addition of malononitrile (see Scheme 11).



Scheme 10

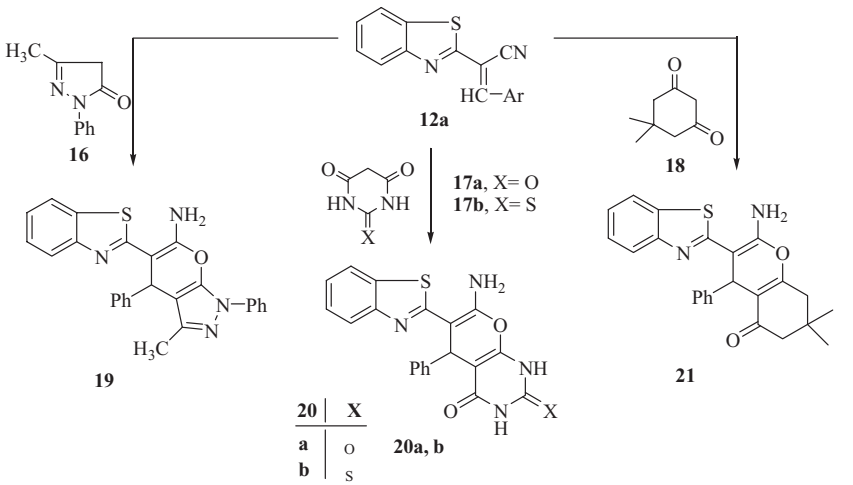


Scheme 11

In these polyfunctionalized pyrido[2,1-b]benzothiazoles, it is clear that the substitution pattern at C-3 of the annelated pyridine ring is determined by the structure of the aromatic aldehyde. The analytical, mass spectral, and ^{1}H NMR data are consistent with the structures proposed for the compounds (**14a–g**). For example, the mass spectra of (**14a–g**) showed the molecular ion peak at *m/z* 328 (M^+, 7.3%), 357 ($M^+ - 1$, 15.2%), 362 (M^+, 5.8%), 407 (M^+, 14%), 372 ($M^+ - 1$, 23.3%), 371 (M^+, 65.2%), and 372 (M^+, 60%), respectively. The IR spectra of these compounds showed the expected bands of CN at 2256–2186, NH_2 at 3428–3402 and 3361–3324 cm^{-1}. The ^{1}H NMR spectrum of (**14e**) featured signals at δ 4.65 (s, 1H, CH), 6.70 (s, 2H, NH_2), and 7.2–8.4 (m, 8H, aromatic).

2-Substituted benzothiazoles constitute an important class of compounds for medicinal, agriculture, and organic chemists. The benzothiazole moiety can be found as a common substructure in a large number of compounds with a wide range of biological activities.[15–18] These compounds possess antitumor, antiviral, antimicrobial, and antiglutamate properties.

In view of the synthetic approaches based on unsaturated nitriles as intermediates for the synthesis of various heterocyclic systems, it appeared that 2-benzylidenecyanomethyl-1,3-benzothiazole (**12a**) could conceivably function as precursor to different 2-substituted benzothiazoles. Thus, 2-benzylidenecyanomethyl-1,3-benzothiazole (**12a**) was treated with 1-phenyl-3-methyl-2-pyrazolin-5-one (**16**), barbituric acid (**17a**), thiobarbituric acid (**17b**), and 5,5-dimethyl-1,3-cyclohexanedione (**18**) to give compounds (**19**), (**20a,b**), and (**21**), respectively (see Scheme 12).



Scheme 12

The analytical and spectral data are consistent with the structure proposed for compounds (**19**), (**20a**,**b**), and (**21**). In general, the IR spectra of these products revealed adsorption bands at 3451–3418 and 3380–3324 cm^{-1} for NH_2 group and disappearance of absorption bands for CN group. The mass spectra of (**19**), (**20a**,**b**), and (**21**) showed the molecular ion peak at *m/z* 436 (M^+, 32%), 392 (M^+, 9%), 410 (M^++4, 12%), and 404 (M^+, 8%), respectively.

The ^{1}H NMR spectrum of (**19**) displayed signals at δ 2.36 (s, 3H, CH_3), 4.84 (s, 1H, pyran 4-H), and a complex multiplet at δ 7.20–7.41, corresponding to a total of 16 protons due to aromatic and NH_2.

Formation of (**19**), (**20a**,**b**), and (**21**) could be explained via a mechanism that involves initial Michael addition of (**16**), (**17a**,**b**), and (**18**) to the ylidenic bond in (**12a**) to give an acyclic intermediate, which, cyclized by the nucleophilic attack of the enolic (OH) on the cyanocarbon, followed by tautomerization to the final products.

Compound (**19**) was unambiguously synthesized by an alternative route involving the condensation of 4-benzylidene-1-phenyl-3-methyl-2-pyrazolin-5-one (**22**) with 2-cyanomethylbenzothiazole (**1**) in refluxing ethanolic piperidine.

Formation of (**19**) from (**1**) and (**22**) or from (**12a**) and (**16**) encouraged us to synthesize compound (**19**) via a one-pot reaction. Thus, condensation of 2-cyanomethylbenzothiazole (**1**), benzaldehyde, and 1-phenyl-3-methyl-2-pyrazolin-5-one (**16**) in ethanolic piperidine afforded (**19**). Compounds (**20a,b**) and (**21**) were also obtained via a one-pot reaction by condensation of (**1**), benzaldehyde, and barbituric or thiobarbituric acid and/or dimedone, respectively.

EXPERIMENTAL

All melting points were recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra υ cm^{-1} (KBr) were recorded on Perkin Elmer Infrared Spectrophotometer Model 157, Grating. The ^1H NMR spectra were obtained on a Varian Spectrophotometer at 200 MHz using TMS as an internal reference and DMSO-d_6 as solvent. The mass spectra (EI) were recorded on 70 eV with Kratos MS equipment and/or a Varian MAT 311 A Spectrometer. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The results were found to be in good agreement ($\pm$0.3%) with the calculated values.

Synthesis of Pyrimidobenzothiazole Derivatives (2a–d): General Procedure

A mixture of 2-cyanomethyl-1,3-benzothiazole (**1**) (0.87 g, 0.005 mol), formalin (1 mL, 0.015 mol), benzylamine (0.54 mL, 0.005 mol) or butylamine (0.5 mL, 0.005 mol) or isopropylamine (0.4 mL, 0.005 mol) or cyclohexylamine (0.57 mL, 0.005 mol) in ethanol (10 mL), and drops of glacial acetic acid was heated on a steam bath for 30 min. The reaction mixture was stirred for 3 h at room temperature, then left to stand overnight, and the separated solids were filtered off and crystallized from ethanol to give compounds (**2a–d**), respectively.

Compound (2a): Separated as pale yellow powder in 0.8 g, 53% yield mp 183°C. Analysis: Calcd. For $C_{18}H_{15}N_3S$ (305.40): C, 70.79%; H, 4.95%; N, 13.76%; S, 10.50; Found C, 70.58%; H, 4.73%; N, 13.49%; S, 10.38. IR (cm^{-1}) (KBr): 3055, 2930 (CH aromatic and CH aliphatic), 2155 (CN group), 1603, 1586 (C=C aromatic and C=C aliphatic), 1308, 1254 (C—N). MS (*m/z*), *rel. inten.*: 306 (M^++1, 13%), 305 (M^+, 65%), 214 (9%), 188 (11%), 187 (44%), 186 (59%), 135 (22%), 108 (11%), 91 (100%). ^1H NMR ($CDCl_3$) δ ppm: 8.01–7.51 (m, 9H, aromatic protons), 3.90 (s, 2H, C$\underline{H_2}$-Ph), 3.69 (d, J = 11.5 Hz, 2H, N—C$\underline{H_2}$—N) and 3.0 (d, J = 12.3 Hz, 2H, C$\underline{H_2}$—N).

Compound (2b): Separated as yellow crystals in 0.5 g, 62% yield mp 168–171°C. Analysis: Calcd. For $C_{15}H_{17}N_3S$ (271.38): C, 66.39%; H, 6.31%; N, 15.48%; S, 11.82; Found C, 66.82%; H, 6.53%; N, 15.63%; S, 12.01. IR (cm^{-1}) (KBr): 3042, 2975 (CH aromatic and CH aliphatic), 2168 (CN group), 1621, 1579 (C=C aromatic and C=C aliphatic), 1327, 1286 (C—N). MS (*m/z*), *rel. inten.*: 272 (M^++1, 18%), 271 (M^+, 100%),

188 (22%), 187 (62%), 186 (95%), 160 (15%), 136 (19%), 135 (32%), 108 (15%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.02–7.43 (m, 4H, aromatic protons), 3.67 (d, J = 12.2 Hz, 2H, N−$\underline{CH_2}$−N) 2.97 (d, J = 12.2 Hz, 2H, Ha, −$\underline{CH_2}$−N) 2.72 (t, 2H, N−$\underline{CH_2}$−$(CH_2)_2$−CH_3), 1.50 (m, 2H, N−CH_2−$\underline{CH_2}$−CH_2CH_3) 1.24 (m, 2H, N−CH_2−CH_2−$\underline{CH_2}$−CH_3) and 0.95 (t, 3H, −$\underline{CH_3}$).

Compound (2c): Separated as yellow crystals in 1.0 g, 78% yield mp 193°C. Analysis: Calcd. For $C_{14}H_{15}N_3S$ (257.35): C, 65.34%; H, 5.87%; N, 16.33%; S, 12.46; Found C, 65.17%; H, 5.59%; N, 16.43%; S, 12.11. IR (cm^{-1}) (KBr): 3089, 2970 (CH aromatic and CH aliphatic), 2125 (CN group), 1644, 1619, 1598 (C=C aromatic and C=C aliphatic), 1487, 1413, 1328 (C−N). MS (*m/z*), *rel. inten.*: 257 (M^+, 43%), 214 ($M^+ - 1$, isopropyl, 4%), 188 (13%), 187 (43%), 186 (100%), 185 (12%), 160 (12%), 159 (17%), 136 (14%), 135 (44%), 108 (20%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.03–7.45 (m, 4H, aromatic protons), 3.63 (d, 2H, Hb, J = 11.5 Hz, N−$\underline{CH_2}$−N) 3.09 (d, 2H, Ha, J = 12.2 Hz, −N−$\underline{CH_2}$) 3.17 (m, 1H, $\underline{CH}$−$(CH_3)_2$) and 1.17 (d, 6H, J = 6.15 Hz, $2CH_3$).

Compound (2d): Separated as yellow crystals in 0.5 g, 34% yield mp 109°C. Analysis: Calcd. For $C_{17}H_{19}N_3S$ (297.42): C, 68.65%; H, 6.44%; N, 14.13%; S, 10.78; Found C, 68.42%; H, 6.17%; N, 14.03%; S, 10.54. IR (cm^{-1}) (KBr): 3070, 2927 (CH aromatic and CH aliphatic), 2194 (CN group), 1600, 1501 (C=C aromatic and C=C aliphatic), 1452, 1434, 1314, 1255 (C−N). MS (*m/z*), *rel. inten.*: 298 (M^++1, 3%), 297 (M^+, 9.7%), 187 (13%), 186 (21%), 136 (10.6%), 135 (21.5%), 108 (10.56%), 69 (13.7%), 68 (21.1%), 67 (8.3%), 55 (100%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.02–7.45 (m, 4H, aromatic protons), 3.69 (d, 2H, J = 12.25 Hz, N−$\underline{CH_2}$−N) 3.01 (d, 2H, J = 12 Hz, N−$\underline{CH_2}$) 2.73 (m, 1H, $\underline{CH}$ (cyclohexyl)), 1.84–1.31 (complex pattern, 10H, cyclohexane).

Synthesis of 2,4-Di(benzothiazol-2(3*H*)-ylidene)pentanedinitrile (3)

A mixture of 2-cyanomethyl-1,3-benzothiazole (**1**) (0.87 g, 0.005 mol), formalin (0.05 mL, 0.006 mol), piperidine (0.5 mL, 0.005 mol) or morphline (0.5 mL, 0.005 mol) in ethanol (10 mL), and drops of glacial acetic acid was heated on a steam bath for 30 min. The reaction mixture was stirred for 3 h at room temperature, then the same procedure as described before was followed. The product obtained was recrystallized from DMF/ethanol (1:3).

Compound (3): Separated as yellowish crystals in 1.15 g, 64% yield mp 158°C. Analysis: Calcd. For $C_{19}H_{12}N_4S_2$ (360.46): C, 63.31%; H, 3.36%; N, 15.54%; S, 17.79; Found C, 63.43%; H, 3.19%; N, 15.24%; S, 17.55. IR (cm^{-1}) (KBr): 3315 (NH), 3020, 2986 (CH aromatic and CH aliphatic), 2228 (CN group), 1421, 1317, 1267 (C−N), 1053, 937, 783 and 712 cm^{-1}. MS (*m/z*), *rel. inten.*: 360 (M^+, 16.21%), 359 ($M^+ - 1$, 27.8%), 358 ($M^+ - 2$, 100%), 225 (23%), 223 (44.4%), 186 (27%), 135 (80.6%), 109 (15.1%), 108 (30.6%), 69 (44.4%). ^{1}H NMR ($CDCl_3$) δ ppm: 9.23 (br. S, 2H, 2NH), 3.62 (s, 2H, CH_2), 8.11–7.20 (m, 8H, aromatic protons).

Synthesis of 4-Cyano-1-aryl-3*H*-pyrido[2,1-b][1,3]benzothiazoles (6a,b) and Quinolino[2,1-b]benzothiazole (9)

Method A. A mixture of 2-cyanomethyl-1,3-benzothiazole (**1**) (0.87 g, 0.005 mol) and 3-(dimethylamino)-1-phenylpropane-1-one hydrochloride (**5a**) (1.0 g, 0.005 mol) or 2-acetylthiophene Mannich base hydrochloride (**5b**) (1.1 g, 0.005 mol) or

cyclohexanone-2-yl methyl dimethylamine hydrochloride (**8b**) (0.95 g, 0.005 mol) in ethanol (15 mL) and glacial acetic acid (3 mL) was heated on a steam bath for 30 min. The reaction mixture was stirred for 8 h at room temperature (TLC control), then left to stand at room temperature overnight. The obtained products were filtered off and subjected to column chromatography on silica gel (pet.ether:ethylacetate 7:3) for (**6a**), (ether:ethylacetate 9:1) for (**6b**), and (*n*-hexane:ether 6:4) for (**9**).

Method B. A mixture of (**1**) (0.87 g, 0.005 mol) and bis Mannich bases (**7a**) (0.83 g, 0.0025 mol) or (**7b**) (0.86 g, 0.0025 mol) or (**8b**) (1.43 g, 0.005 mol) in ethanol (15 mL) and glacial acetic acid (3 mL) was heated and worked up as above to give compounds (**6a, b**) and (**9**), respectively.

Compound (6a): Separated as pale green crystals in 0.6 g, 70% yield mp 98–100°C. Analysis: Calcd. For $C_{18}H_{12}N_2S$ (288.37): C, 74.97%; H, 4.19%; N, 9.71%; S, 11.12; Found C, 74.63%; H, 4.38%; N, 9.54%; S, 10.93. IR (cm^{-1}) (KBr): 3061, 2923 (CH aromatic and CH aliphatic), 2192 (CN group), 1645, 1414 (C=C aromatic and C=C aliphatic), 1453, 1300 (C−N) and 753 cm^{-1}. MS (*m/z*), *rel. inten.*: 289 (M^++1, 31.9%), 290 (M^++2, 27.5%), 213 (11.9%), 212 (18.3%), 211 (100%), 210 (23%). ^{1}H NMR ($CDCl_3$) δ ppm: 7.99–6.62 (m, 9H, aromatic protons), 3.32 (t, 1H, C=C−H), 3.22 (d, 1H, Ha, J = 8.2 Hz) and 3.09 (d, 1H, Ha', J = 8.6 Hz).

Compound (6b): Separated as brown crystals in 0.5 g, 57% yield mp 140–142°C. Analysis: Calcd. For $C_{16}H_{10}N_2S_2$ (294.39): C, 65.28%; H, 3.42%; N, 9.52%; S, 21.78; Found C, 65.01%; H, 3.17%; N, 9.26%; S, 21.59. IR (cm^{-1}) (KBr): 3062, 2924 (CH aromatic and CH aliphatic), 2185 (CN group), 1620, 1578 (C=C aromatic and C=C aliphatic), 1433, 1313 (C−N), 758 and 728 cm^{-1}. MS (*m/z*), *rel. inten.*: 295 (M^++1, 6%), 294 (M^+, 4.3%), 277 (7.3%), 176 (38.4%), 131 (10.3%), 105 (84.7%), 78 (11%), 77 (100%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.04–7.53 (m, 7H, aromatic and thiophen protons), 3.68 (t, 1H, C=C−H), 3.53 (d, 1H, Ha, J = 6.6 Hz) and 3.49 (d, 1H, Ha′, J = 6.6 Hz).

Compound (9): Separated as pale brown crystals in 0.4 g, 47% yield mp 80–82°C. Analysis: Calcd. For $C_{16}H_{16}N_2OS$ (284.38): C, 67.58%; H, 5.67%; N, 9.85%; S, 11.28; Found C, 67.83%; H, 5.39%; N, 9.64%; S, 11.46. IR (cm^{-1}) (KBr): 3452 (OH group), 3064, 2971 (CH aromatic and CH aliphatic), 2179 (CN group), 1598, 1573 (C=C aromatic and C=C aliphatic), 1434, 1313 (C−N), 1244, 1011, 756 and 726 cm^{-1}. MS (*m/z*), *rel. inten.*: 284 (M^+, 57.5%), 283 ($M^+ - 1$, 100%), 282 ($M^+ - 2$, 37.5%), 267 (75%), 265 (67.6%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.1 (br. S, 1H, OH), 7.59–7.32 (m, 9H, aromatic protons), 2.07 (dd, 2H, allylic protons), 1.9–1.4 (m, 9H, hexan ring protons).

Synthesis of 1-Amino-2,4-dicyano-3-aryl-3*H*-pyrido[2,1-b] benzothiazoles (14a–g)

A mixture of 2-cyanomethyl-1,3-benzothiazole (**1**) (1.74 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol), and benzaldehyde (1.06 g, 0.01 mol) or *p*-anisaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.4 g, 0.01 mol) or 4-bromobenzaldehyde (1.85 g, 0.01 mol) or 4-nitrobenzaldehyde (1.5 g, 0.01 mol) or 4-(dimethylamino)benzaldehyde (1.5 g, 0.01 mol) or piperonal (1.5 g, 0.01 mol) in ethanol (15 mL) with triethylamine (3–4 drops) was refluxed on a water bath for 3 h (TLC control). The reaction mixture was left to stand at room temperature for 1 h. The obtained products were filtered off and recrystallized from ethanol to give compounds (**14a–g**), respectively.

Compound (14a): Separated as yellow crystals in 2.6 g, 79% yield mp 197–198°C [lit. 190–191°C[14]]. Analysis: Calcd. For $C_{19}H_{12}N_4S$ (328.39): C, 69.49%; H, 3.68%; N,

17.06%; S, 9.76; Found C, 69.71%; H, 3.39%; N, 16.89%; S, 9.49. IR (cm^{-1}) (KBr): 3418, 3324 (NH_2 group), 3075, 2892 (CH aromatic and CH aliphatic), 2186 (CN group), 1643, 1616 (C=C aromatic and C=C aliphatic), 1552, 1451, 1408, 1321 (C−N). MS (*m/z*), *rel. inten.*: 329 (M^++1, 2.3%), 328 (M^+, 7.3%), 327 ($M^+ - 1$, 28.2%), 326 ($M^+ - 2$, 100%), 300 (14.3%), 299 (48.8%). ^{1}H NMR ($CDCl_3$) δ ppm: 7.36–7.25 (m, 11H, aromatic protons + 2H, NH_2), 4.60 (s, 1H, Ha).

Compound (14b): Separated as greenish yellow crystals in 2.5 g, 70% yield mp 189–191°C [lit. 193–194°C[14]]. Analysis: Calcd. For $C_{20}H_{14}N_4OS$ (358.42): C, 67.02%; H, 3.94%; N, 15.63%; S, 8.95; Found C, 67.23%; H, 3.65%; N, 15.41%; S, 8.48. IR (cm^{-1}) (KBr): 3418, 3324 (NH_2 group), 3056, 2972 (CH aromatic and CH aliphatic), 2221 (CN group), 1608, 1590 (C=C aromatic and C=C aliphatic), 1513, 1420, 1319, 1279 (C−N), 1181, 1023 (C−O). MS (*m/z*), *rel. inten.*: 357 ($M^+ - 1$, 15.22%), 356 (14.13%), 332 (39.13%), 331 (26%), 317 (65.2%), 318 (16.3%), 316 (22.83%), 300 (37%), 299 (30%). ^{1}H NMR ($CDCl_3$) δ ppm: 7.74–6.87 (m, 10H, aromatic protons + 2H, NH_2), 4.55 (s, 1H, CH), 3.797 (s, 3H, OMe), 1.699 (br. S, 2H, NH_2).

Compound (14c): Separated as yellow crystals in 3 g, 83% yield mp 212–213°C [lit. 210–211°C[14]]. Analysis: Calcd. For $C_{19}H_{11}ClN_4S$ (362.84): C, 62.89%; H, 3.06%; Cl, 9.77%; N, 15.44%; S, 8.84; Found C, 62.57%; H, 3.14%; Cl, 9.52%; N, 15.63%; S, 8.47. IR (cm^{-1}) (KBr): 3415, 3365 (NH_2 group), 3055, 2991 (CH aromatic and CH aliphatic), 2252 (CN group), 1600, 1590 (C=C aromatic and C=C aliphatic), 1514, 1433, 1383, 1306, 1277 (C−N) and 729 (C−Cl). MS (*m/z*), *rel. inten.*: 362 (M^+, 5.8%), 361 ($M^+ - 1$, 3%), 360 (5.57%), 298 (20.4%), 297 (49%), 296 (41.3%), 295 (10%), 270 (16.4%), 261 (11%), 251 (19.7%), 174 (25%), 125 (16%), 107 (12%), 99 (5.3%), 82 (10%), 75 (8.9%), 69 (18.2%), 66 (6.8%), 63 (10.1%).

Compound (14d): Separated as pale yellow crystals in 3.1 g, 76% yield mp 139°C. Analysis: Calcd. For $C_{19}H_{11}BrN_4S$ (407.29): C, 56.03%; H, 2.72%; Br, 19.62; N, 13.76%; S, 7.87; Found C, 55.87%; H, 2.62%; Br, 19.43; N, 13.54%; S, 7.61. IR (cm^{-1}) (KBr): 3325 (NH_2 group), 3077, 2933, 2850 (CH aromatic and CH aliphatic), 2085 (CN group), 1625, 1583 (C=C aromatic and C=C aliphatic), 1484, 1338 (C−N), 1230, 850, 727, 701 and 650 (C−Br) cm^{-1}. MS (*m/z*), *rel. inten.*: 408 (M^++1, 15.1%), 407 (M^+, 14%), 406 (29.7%), 405 (11.5%), 404 (18.8%), 341 (73.8%), 339 (69.3%), 259 (15.7%), 253 (76%), 252 (16.8%), 251 (100%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.19–7.65 (m, 10H, aromatic protons + 2H, NH_2), 4.64 (s, 1H, Ha).

Compound (14e): Separated as reddish brown crystals in 3.2 g, 86% yield mp 148°C. Analysis: Calcd. For $C_{19}H_{11}N_5O_2S$ (373.39): C, 61.12%; H, 2.97%; N, 18.76%; S, 8.59; Found C, 61.34%; H, 2.58%; N, 18.61%; S, 8.39. IR (cm^{-1}) (KBr): 3382, 3351 (NH_2 group), 3051, 2954 (CH aromatic and CH aliphatic), 2256 (CN group), 1610, 1573, 1451, 1362, 1307 (N=O), 1343, 1276, 1240 (C−N). MS (*m/z*), *rel. inten.*: 373 (M^+, 7.6%), 372 ($M^+ - 1$, 23.3%), 371 ($M^+ - 2$, 90.5%), 354 (13.7%), 344 (10%), 324 (26.25%), 307 (54.84%), 306 (100%). ^{1}H NMR ($CDCl_3$) δ ppm: 8.42–7.27 (m, 10H, aromatic protons + 2H, NH_2), 4.65 (s, 1H, CH).

Compound (14f): Separated as red crystals in 2.8 g, 76% yield mp 226°C. Analysis: Calcd. For $C_{21}H_{17}N_5S$ (371.46): C, 67.90%; H, 4.61%; N, 18.85%; S, 8.63; Found C, 67.70%; H, 4.33%; N, 18.61%; S, 8.43. IR (cm^{-1}) (KBr): 3421, 3351 (NH_2 group), 3058, 2954, 2923 (CH aromatic and CH aliphatic), 2186 (CN group), 1635, 1602, (C=C aromatic and C=C aliphatic), 1454, 1322, 1301 (C−N). MS (*m/z*), *rel. inten.*: 371 (M^+, 65.2%), 327 (22.52%), 301 (75.1%), 275 (20.62%), 266 (100%), 259 (42.51%), 169 (75.27%), 152 (65.13%), 106 (25.14%), 105 (25.2%), 91 (77.52%), 62 (20.01%). ^{1}H NMR

($CDCl_3$) δ ppm: 8.15–7.25 (m, 9H, aromatic protons + 2H, NH_2), 3.11 (s, 6H, 2Methyl group).

Compound (14g): Separated as yellow crystals in 2.9 g, 78% yield mp 219°C. Analysis: Calcd. For $C_{20}H_{12}N_4O_2S$ (372.40): C, 64.50%; H, 3.25%; N, 15.04%; S, 8.61; Found C, 64.81%; H, 3.02%; N, 15.26%; S, 8.43. IR (cm^{-1}) (KBr): 3402, 3366 (NH_2 group), 3042, 2961 (CH aromatic and CH aliphatic), 2220 (CN group), 1611, 1596 (C=C aromatic and C=C aliphatic), 1502, 1463, 1312, 1277 (C−N). MS (*m/z*), *rel. inten.*: 372 (M^+, 60.02%), 371 (M^++1, 20.1%), 320 (20.31%), 306 (77.8%), 305 (100%), 280 (62.51%), 247 (75.01%), 246 (27.49%). ^1H NMR ($CDCl_3$) δ ppm: 8.14–7.43 (m, 7H, aromatic protons), 7.25 (s, 2H, NH_2), 6.93 (s, 1H, C<u>H</u>), 6.09 (s, 2H, −O−C<u>H_2</u>−O).

Synthesis of 5-(Benzo[d]thiazol-2-yl)-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-c]pyrazol-6-amine (19), 7-Amino-6-(benzo[d]thiazol-2-yl)-2,3-dihydro-5-phenyl-2-oxo-1*H*-pyrano[2,3-d]pyrimidin-4(5*H*)-one (20a), 7-Amino-6-(benzo[d]thiazol-2-yl)-2,3-dihydro-5-phenyl-2-thioxo-1*H*-pyrano[2,3-d]pyrimidin-4(5*H*)-one (20b), and 2-Amino-3-(benzo[d]thiazol-2-yl)-7,8-dihydro-7,7-dimethyl-4-phenyl-4*H*-chromen-5(6*H*)-one (21)

Equimolar amounts of 2-benzylidenecyanomethyl-1,3-benzothiazole (**12a**)[14] (1.31 g, 0.005 mol) and 2-pyrazoline-5-one (**16**) (0.87 g, 0.005 mol), barbituric acid (**17a**) (0.6 g, 0.005 mol), thiobarbituric acid (**17b**) (0.7 g, 0.005 mol), or dimedone (**18**) (0.7 g, 0.005 mol) in ethanol (15 mL) and triethyl amine (3–4 drops) were then added and refluxed on a steam bath for 3 h (TLC control). The reaction mixture was left to stand at room temperature overnight, and the obtained products were filtered off and recrystallized from ethanol to give compounds (**19**), (**20a**), (**20b**), and (**21**), respectively.

Compound (19): Separated as brown crystals in 2 g, 46% yield mp 190°C. Analysis: Calcd. For $C_{26}H_{20}N_4OS$ (436.53): C, 71.54%; H, 4.62%; N, 12.83%; S, 7.35; Found C, 71.73%; H, 4.35%; N, 12.66%; S, 7.13. IR (cm^{-1}) (KBr): 3418, 3324 (NH_2 group), 3053, 2961 (CH aromatic and CH aliphatic), 1643 (C=N), 1616, 1578 (C=C aromatic and C=C aliphatic), 1552, 1451, 1408, 1321, 1299 (C−N), 1172 (C−O). MS (*m/z*), *rel. inten.*: 436 (M^+, 31.43%), 359 (71.42%), 302 (11.5%), 263 (48.57%), 262 (37.14%), 261 (100%), 174 (54.29%), 146 (11.43%), 108 (20.02%), 69 (51.43%), 63 (57%), 51 (25.71%). ^1H NMR ($CDCl_3$) δ ppm: 7.41–7.20 (m, 16H, aromatic protons + 2H, NH_2), 4.84 (s, 1H, C<u>H</u>), 2.36 (s, 3H, CH_3).

Compound (20a): Separated as pale brown crystals in 1.8 g, 92% yield mp 205°C. Analysis: Calcd. For $C_{20}H_{14}N_4O_3S$ (390.42): C, 61.53%; H, 3.61%; N, 14.35%; S, 8.21; Found C, 61.75%; H, 3.36%; N, 14.12%; S, 8.41. IR (cm^{-1}) (KBr): 3444, 3388 (NH_2 group), 3027, 2954 (CH aromatic and CH aliphatic), 1689 (CO), 1572 (C=N), 1376, 1301 (C−N), 1049, 944 (C−O). MS (*m/z*), *rel. inten.*: 392 (M^++2, 9%), 352 (92.3%), 352 (92.31%), 350 (69.23%), 328 (69.23%), 326 (61.54%), 304 (76.92%), 282 (69.23%), 268 (76.92%), 221 (76.92%), 214 (69.23%), 197 (61.54%), 176 (61.54%), 174 (61.54%), 156 (84.62%), 122 (76.92%), 111 (100%), 108 (76.92%), 102 (69.23%), 67 (69.23%), 63 (61.54%), 61 (61.54%).

Compound (20b): Separated as white-brown crystals in 1.8 g, 89% yield mp 277°C. Analysis: Calcd. For $C_{20}H_{14}N_4O_2S_2$ (406.48): C, 59.10%; H, 3.47%; N, 13.78%; S, 15.78; Found C, 58.95%; H, 3.24%; N, 13.50%; S, 15.53. IR (cm^{-1}) (KBr): 3446, 3407 (NH_2), 3070, 2950 (CH aromatic and CH aliphatic), 1720 (CO), 1697 (C=S), 1644, 1617, (C=C aromatic and C=C aliphatic), 1569 (C=N), 1434, 1384, 1349, 1294 (C−N), 1240, 1157,

927 (C—O). MS (*m/z*), *rel. inten.*: 410 (M^++4, 12%), 233 (18.4%), 232 (18.4%), 232 (100%), 231 (85.6%), 174 (5.12%), 172 (25.53%), 146 (8.2%), 145 (7.35%), 144 (71.7%).

Compound (21): Separated as gray crystals in 1.5 g, 75% yield mp 177–178°C. Analysis: Calcd. For $C_{24}H_{12}N_4O_2S$ (402.51): C, 71.62%; H, 5.51%; N, 6.96%; S, 7.97; Found C, 71.83%; H, 5.72%; N, 6.64%; S, 7.69. IR (cm^{-1}) (KBr): 3421, 3351 (NH_2), 3056, 2455 (CH aromatic and CH aliphatic), 1743 (CO), 1662, 1616, (C=C aromatic and C=C aliphatic), 1540 (C=N), 1479, 1450, 1373, 1284 (C—N), 1160, 1124, 933 (C—O). MS (*m/z*), *rel. inten.*: 404 (M^++2, 3.25%), 403 (M^++1, 11.6%), 402 (M^+, 8%), 327 (7.5%), 325 (100%). ^{1}H NMR ($CDCl_3$) δ ppm: 7.81–7.03 (m, 11H, aromatic protons + 2H, NH_2), 4.84 (s, 1H, C<u>H</u>), 2.49 (s, 2H, —CH—CO), 2.26 (s, 2H, CH_2), 1.14 (s, 3H, Me), 0.97 (s, 3H, Me).

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