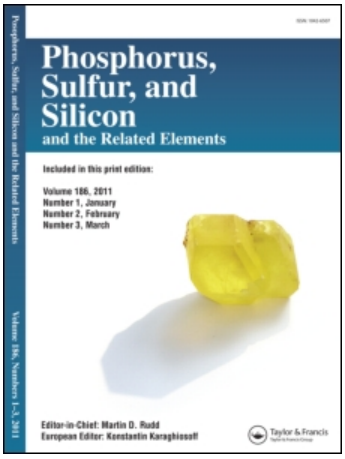

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Synthesis of Some Novel Benzothiazole Derivatives

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Novel 1,2,4-triazine, pyridine, and benzopyran derivatives have been synthesized from N-(2-benzothiazolyl)cyanoacetamide via its reaction with some electrophiles. The structure of the synthesized compounds was established by analytical and spectral data.

Keywords 1,2,4-triazine; benzothiazole; pyridine, and benzopyran derivatives

INTRODUCTION

The introduction of various heterocyclic moieties at position 2 of the benzothiazole nucleus is beneficial for antimicrobial,[1,2] antifungal,[3] antimalarial,[4] antitumor,[5] antiinflammatory,[6] histamine H_3 antagonist,[7] and diabetes[8] activities. Also, benzothiazoles are commercially important as reactive dyes,[9] hair dyes,[10] agrochemical fungicides, insecticides, acaricides,[11] herbicides, plant desiccants and defolicants.[12] In continuation of our program directed for the development of a new, simple, and efficient procedure for the synthesis of biologically active heterocyclic compounds utilizing readily obtainable intermediates,[13–16] we have investigated the reaction of *N*-(2-benzothiazolyl)cyanoacetamide (**4**) with some electrophilic reagents for the synthesis of some novel 1,2,4-triazine, pyridine and benzopyran derivatives.

RESULTS AND DISCUSSION

Stetinova et al.[17] have reported the synthesis of *N*-(2-benzo-thiazolyl)cyanoacetamide (**4**) by condensation of cyano-acetohydrazide (**1**) with acetylacetone to furnish 1-cyanoacetyl-3,

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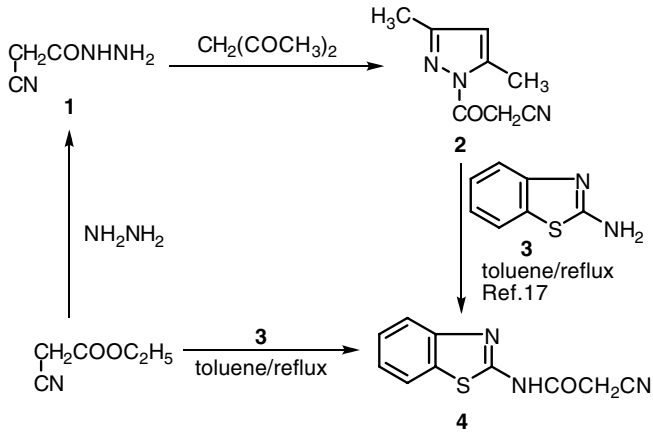
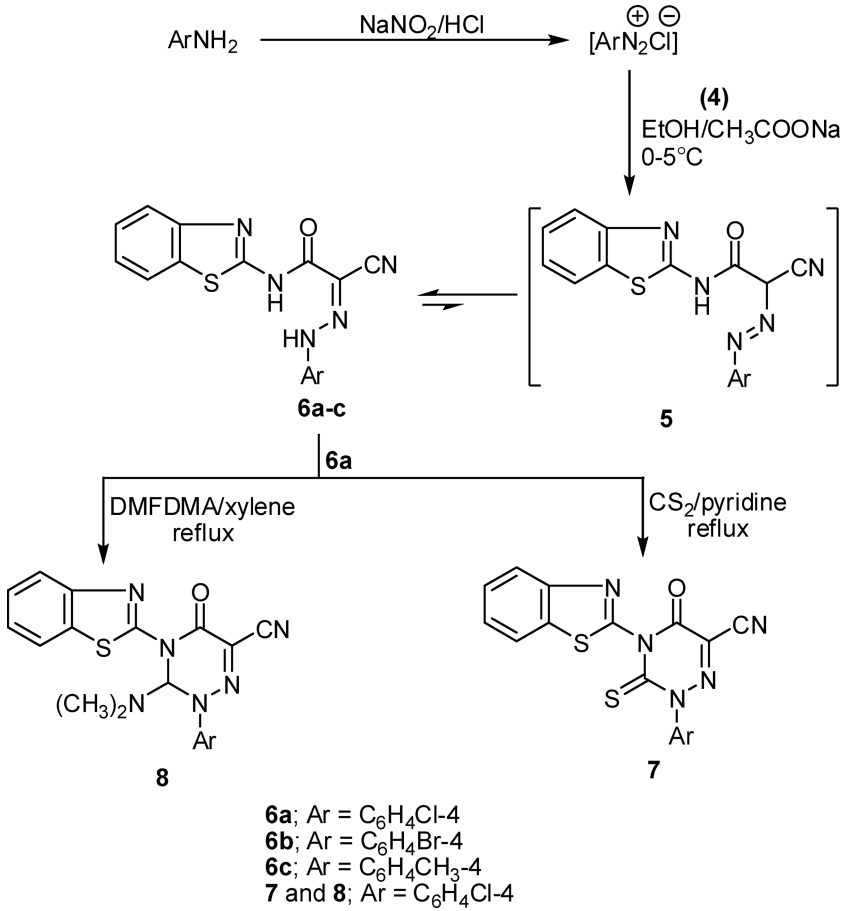
5-dimethylpyrazole (**2**) followed by treatment with 2-aminobenzothiazole (**3**) in boiling toluene. In our investigation, cyanoacetamide derivative (**4**) was synthesized in one step by condensation of ethyl cyanoacetate with 2-aminobenzothiazole (**3**) in toluene at reflux temperature in quantitative yield (95%) (Scheme 1).



SCHEME 1

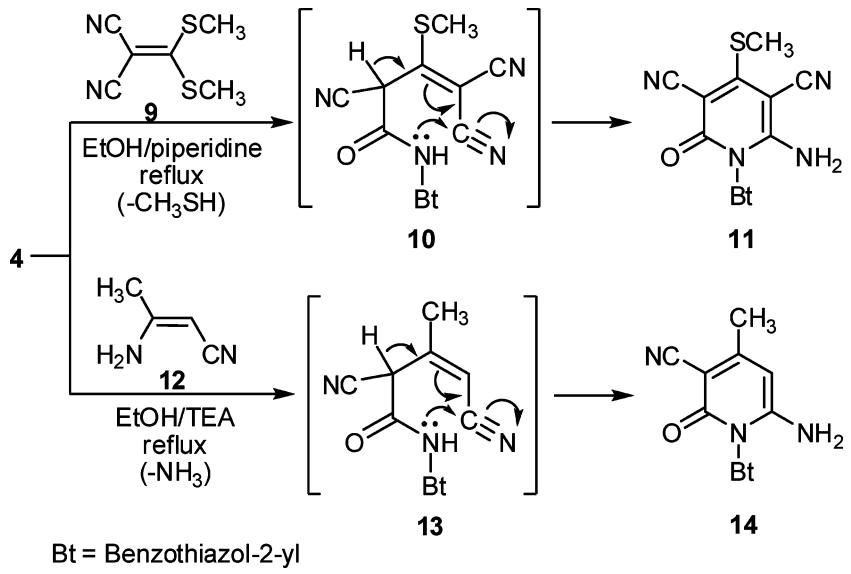
Cyanoacetamide derivative (**4**) was used as a key intermediate for the synthesis of hitherto unknown benzothiazole derivatives through its reaction with some electrophilic reagents. Diazotization of aromatic amines followed by coupling with active methylene group in compound (**4**) in ethanol in the presence of sodium acetate yielded the hydrazone form (**6**) rather than the azo form (**5**) based on spectral data. The ^{1}H NMR spectrum of compound (**6c**) recorded in DMSO-d_6 revealed a signal at δ 9.97 ppm, which could be attributed to hydrazone NH group. Cyclocondensation of compound (**6a**) with carbon disulfide in pyridine[18] at reflux temperature furnished the novel 1,2,4-triazinone derivative (**7**) in acceptable (74%) yield. The structure of the latter product was established based on analytical and spectral data. Its infrared spectrum was characterized by disappearance of NH group and showed an absorption band at 2218 cm^{-1} due to the C≡N group. The formation of (**7**) is assumed to proceed via initial nucleophilic attack of the secondary amino group of **5** to the thiocarbonyl group of the carbon disulfide followed by intramolecular cyclization through elimination of hydrogen sulfide.[18] The 1,2,4-triazinone derivative (**8**) was obtained by treatment of compound (**6a**) with dimethylformamide-dimethylacetal (DMFDMA) in dry *m*-xylene under reflux. The molecular structure of compound (**8**) was established by analytical and spectral data. The infrared spectrum

of compound (**8**) indicated the absence of the NH group and its ^{1}H NMR spectrum recorded in DMSO-d_6 exhibited a signal characteristic for *N*, *N*-dimethyl protons. The formation of the latter product is assumed to proceed through addition of the secondary amino group in compound (**6a**) to the electrophilic carbon atom in DMFDMA with elimination of methanol followed by intramolecular cyclization by loss of methanol to give (**8**) (Scheme 2).



SCHEME 2

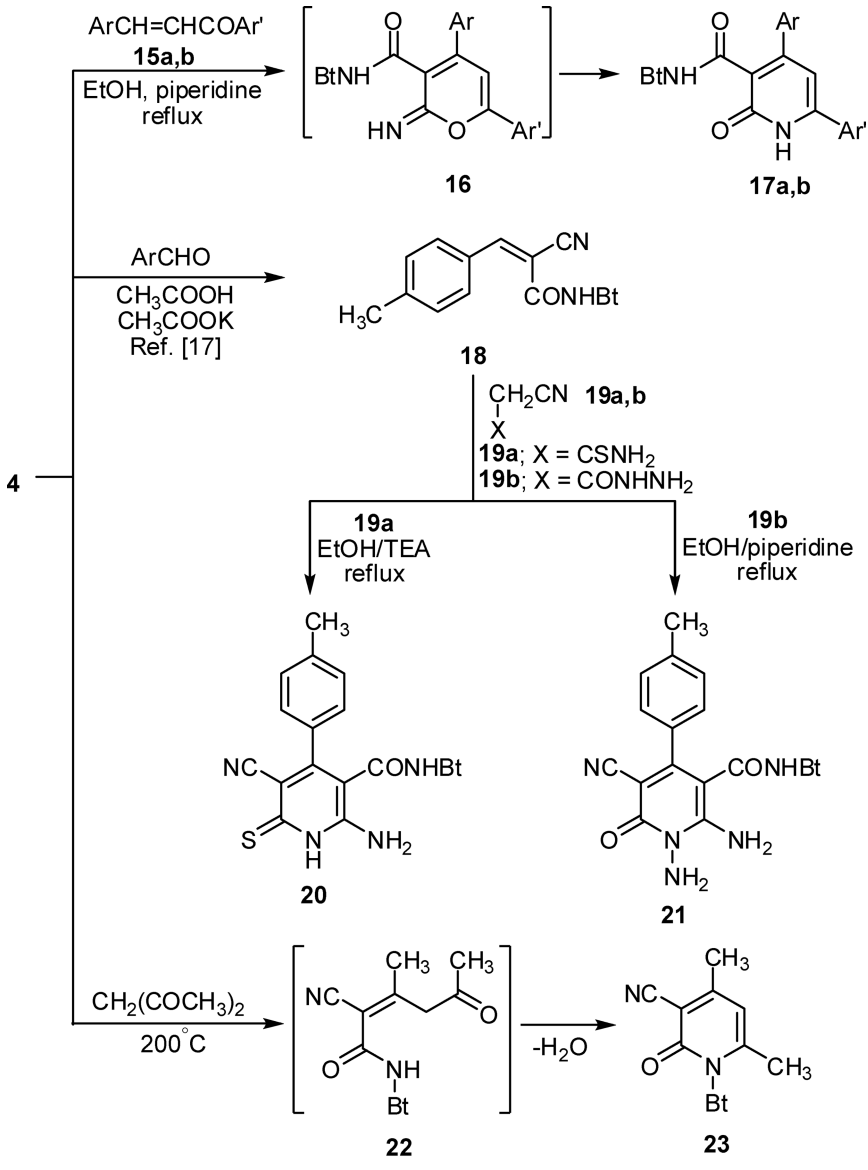
Cyclocondensation of compound (**4**) with ketene dithioacetal (**9**) in refluxing ethanol as solvent and catalytic amounts of piperidine yielded the pyridinone derivative (**11**) in good yield (88%). The structure of compound (**11**) was confirmed based on its analytical and spectral data.



SCHEME 3

Thus, the ^{1}H NMR spectrum showed the presence of a singlet for the protons of the thiomethyl group at δ 1.78 ppm in addition to the signals of the amino and aromatic protons. The formation of (**11**) is assumed to proceed via Michael addition of the active methylene function in (**4**) to ketene (**9**) and elimination of methyl mercaptan to form non-isolable intermediate (**10**) followed by intra-molecular cyclization[19] and tautomerization to furnish (**11**), Scheme 3. Treatment of compound (**4**) with 3-aminocrotononitrile (**12**) in ethanol in the presence of triethylamine under reflux furnished the pyridinone derivative (**14**). The molecular structure of (**14**) was established based on its elemental analysis and spectral data. Its infrared spectrum showed absorption bands at 3269, 3114 cm^{-1} due to NH_2 group in addition to the two absorption bands at 2203 and 1666 cm^{-1}, which can be assigned to C≡N and C=O, respectively. In addition, its ^{1}H NMR spectrum in DMSO-d_6 displayed signals characteristic for amino, pyridine, methyl, and aromatic protons. The formation of (**14**) was assumed to be processed via the intermediate (**13**) followed by intramolecular cyclization[20] through nucleophilic addition of the secondary amino group to the cyano group and tautomerization (Scheme 3).

The reaction of (**4**) with α,β-unsaturated ketones (**15a**, **b**) in the presence of catalytic amount of piperidine led to the formation of pyridinone derivatives (**17a**, **b**). The formation of (**17**) is assumed



15a and **17a**; Ar = $C_6H_4OCH_3$-2, Ar' = C_6H_5
b; Ar = C_6H_4Cl-4, Ar' = C_6H_5
Bt = Benzothiazol-2-yl

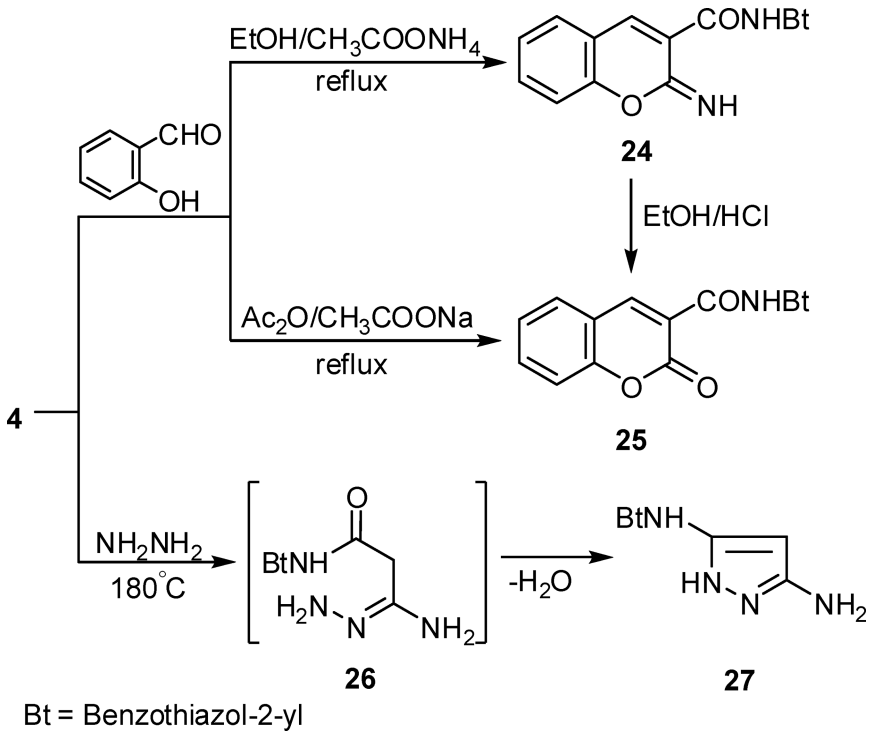
SCHEME 4

to proceed via Michael addition of the active methylene function in (**4**) to the activated double bond in (**15**) followed by intramolecular cyclization to furnish pyran (**16**) which was subjected to Dimroth rearrangement[20] (Scheme 4). Benzylidene derivative (**18**) was obtained by treatment of (**4**) with 4-methyl benzaldehyde in refluxing acetic acid in the presence of potassium acetate.[17] Reaction of benzylidene derivative (**18**) with cyanothioacetamide (**19a**) under reflux in ethanol in the presence of catalytic amount of triethylamine afforded the pyridinethione derivative (**20**) in quantitative yield. The formation of (**20**) is assumed to proceed via Michael addition of the active methylene function in (**4**) to the double bond in (**18**) followed by intramolecular cyclization and autoxidation,[19] under the reaction conditions. In a similar manner, cyclization of benzylidene derivative (**18**) with cyanoacetic acid hydrazide (**19b**) in ethanol at reflux temperature in the presence of piperidine produced the *N*-aminopyridinone derivative (**21**). 4,6-Dimethyl-2-oxo-1-(benzothiazol-2-yl)-1,2-dihydro-pyridine-3-carbonitrile (**23**) was achieved by the reaction of (**4**) with acetylacetone at 200°C in the absence of solvent, via intermediate formation (**22**) followed by elimination of water, Scheme 4.

Some benzopyran derivatives possessing a carboxamide moiety are found to have antibacterial,[21] diuretic, analgesic, myorelaxant,[22] and antifungal[23] activities. Thus, 3-(2-benzothiazolyl) carboxamide-2*H*-1-benzopyran-2-imine (**24**) was synthesized by the cyclocondensation of compound (**4**) with salicylaldehyde in ethanol in the presence of ammonium acetate. The product was identified by spectroscopy and elemental analysis. Its infrared spectrum revealed the absence of the C≡N group. On the other hand, the reaction of (**4**) with salicylaldehyde in acetic anhydride in the presence of fused sodium acetate furnished benzopyran derivative (**25**). The structure of compound (**25**) was established based on its elemental analysis, spectral data and an independent synthesis through conversion of imino group in compound (**24**) to a carbonyl group with hydrochloric acid at room temperature. Treatment of compound (**4**) with hydrazine hydrate furnished amino pyrazole derivative (**27**), via intermediate formation (**26**) followed by intramolecular cyclization through elimination of water, Scheme 5.

CONCLUSION

In conclusion, we have found a facile method for the synthesis of *N*-(2-benzothiazolyl)cyanoacetamide **4**. Also, the reaction of cyanoacetamide derivative **4** with some electrophilic reagents was investigated.



SCHEME 5

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini spectrometer 200 (200 MHz), using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are given in δ ppm. Microanalytical data were obtained from the Microanalytical Unit at Cairo University. Found: C, H, N for all compounds were within $\pm$ 0.4% from theoretical value. Physical data for the synthesized compounds are given in Table I. Also, the spectral data are collected in Table II.

N-(2-Benzothiazolyl)cyanoacetamide (4)

A mixture of ethyl cyanoacetate (0.01 mol) and 2-aminobenzothiazole **3** (0.01 mol) in toluene (20 mL) was refluxed for 5 h, the solid product

TABLE I Physical and Analytical Data of the Synthesized Compounds

	MP (°C)	Solvent cryst.	Yield Color	Molecular formula (%)	(mol. wt)	Elemental analysis C%	H%	N%
6a	238–239	D/E	Yellow	86	$C_{16}H_{10}ClN_5OS$	54.01	2.83	19.68
					(355.81)	54.10	2.80	19.70
6b	242–244	D/E	Yellow	82	$C_{16}H_{10}BrN_5OS$	48.01	2.52	17.50
					(400.26)	48.30	2.50	17.50
6c	240–241	D/E	Yellow	76	$C_{17}H_{13}N_5OS$	60.88	3.91	20.88
					(335.39)	60.80	3.90	20.80
7	252–253	E	Brown	74	$C_{17}H_8ClN_5OS_2$	51.32	2.03	17.60
					(397.87)	51.30	2.00	17.60
8	268–269	D/E	Brown	62	$C_{19}H_{15}ClN_6OS$	55.54	3.68	20.45
					(410.89)	55.50	3.60	20.40
11	>300	DMF/E	Brown	88	$C_{15}H_9N_5OS_2$	53.08	2.67	20.63
					(339.40)	53.10	2.60	20.60
14	298–299	DMF/E	Brown	77	$C_{14}H_{10}N_4OS$	59.56	3.57	19.84
					(282.33)	59.50	3.50	19.80
17a	200–202	D/E	Yellow	77	$C_{26}H_{19}N_3O_3S$	68.86	4.22	9.27
					(453.52)	68.80	4.20	9.20
17b	>300	D	Brown	70	$C_{25}H_{16}ClN_3O_2S$	65.57	3.52	9.18
					(457.94)	65.50	3.50	9.10
20	140–141	E	Pale yellow	88	$C_{21}H_{15}N_5OS_2$	60.41	3.62	16.77
					(417.51)	60.40	3.60	16.70
21	330–332	D/E	Yellow	74	$C_{21}H_{16}N_6O_2S$	60.57	3.87	20.18
					(416.46)	60.50	3.80	20.10
23	232–233	E	Brown	86	$C_{15}H_{11}N_3OS$	64.04	3.94	14.94
					(281.34)	64.10	3.90	14.90
24	170–171	E	Pale yellow	87	$C_{17}H_{11}N_3O_2S$	63.54	3.45	13.08
					(321.36)	63.50	3.40	13.10
25	206–207	E	Brown	82	$C_{17}H_{10}N_2O_3S$	63.35	3.13	8.69
					(322.34)	63.30	3.10	8.70
27	90–91	E	Brown	70	$C_{10}H_9N_5S$	51.93	3.92	30.28
					(231.28)	51.90	3.90	30.20

Where E = Ethanol; D = Dioxane; and DMF = Dimethylformamide.

produced on heating was collected and recrystallized from acetic acid to give **4** as colorless crystals, m.p. 246°C (Lit.[17] m.p. 246–248°C).

N-(2-Benzothiazolyl)-2-arylhydrazono-2-cyanoacetamides (6a–c)—General Procedure

Aromatic amine (0.01 mol) was dissolved in a mixture of concentrated HCl (3 mL) and water (6 mL) and cool to 0°C in an ice bath. A cold

TABLE II Spectral Data of the Synthesized Compounds

	IR/ν_{max}(cm^{-1})	^{1}H NMR (DMSO-d_6) (δ/ppm)
6a	3448, 3292 (NH), 2221 (C≡N), 1689 (C═O; amide).	4.12 (s, 1H, NH), 7.28–7.46 (m, 4H, Ar─H), 7.72, 7.98 (2d, 4H, Ar─H), 7.81 (1H, NH).
6b	3442, 3292 (NH), 2262 (C≡N), 1689 (C═O; amide).	
6c	3420, 3270 (NH), 2170 (C≡N), 1634 (C═O; amide).	2.29 (s, 3H, CH_3), 7.19–7.47 (m, 4H, Ar─H), 7.65, 7.91 (2d, 4H, Ar─H), 7.77 (1H, NH), 9.97 (s, 1H, NH).
7	2218 (C≡N), 1676 (C═O).	7.29–7.99 (m, 8H, Ar─H).
8	2195 (C≡N), 1696 (C═O).	3.23 (s, 6H, $2CH_3$), 7.24–8.24 (m, 8H, Ar─H), 8.87 (s, 1H, triazine-H).
11	3323, 3198 (NH_2), 2935, 2855 (CH-aliph), 2204 (C≡N), 1630 (C═O).	1.78 (s, 3H, SCH_3), 3.90 (2H, NH_2), 7.34–7.99 (m, 4H, Ar─H).
14	3269, 3114 (NH_2), 2926 (CH-aliph), 2203 (C≡N), 1666 (C═O).	2.51 (s, 2, 3H, CH_3), 6.21 (s, 2H, NH_2), 7.22–7.91 (m, 4H, Ar─H), 10.01 (s, 1H, H-pyridine).
17a	3394, 3296 (NH), 2951 (CH-aliph), 1652 (C═O).	—
17b	3398 (NH), 1686 (C═O).	7.30–8.00 (m, 14H, Ar─H), 8.32, 8.36 (2s, 2H, 2NH).
20	3335, 3205 (NH_2), 2940 (CH-aliph), 2214 (C≡N), 1633 (C═O).	1.27 (s, 2H, NH_2), 2.34 (s, 3H, CH_3), 7.13–7.40 (m, 9H, Ar─H + NH), 7.80 (1H, NH).
21	3324, 3300 (NH_2), 2945 (CH-aliph), 2204 (C≡N), 1643 (C═O).	2.34 (s, 3H, CH_3), 3.65 (4H, NH_2), 7.16–7.37 (m, 8H, Ar─H), 9.93 (s, 1H, NH).
23	3075 (CH-arom), 2219 (C≡N), 1675 (C═O).	2.24, 2.48 (2s, 6H, CH_3), 6.19 (s, 1H, pyridine-H), 7.49–8.09 (m, 4H, Ar─H).
24	3259, 3192 (NH), 3060 (CH-arom), 1705 (C═O).	7.0–7.9 (m, 9H, Ar─H), 8.01, 8.70 (2H, 2NH).
25	3421 (NH), 3062 (CH-arom), 1764 (C═O; lactone), 1678 (C═O; amide).	7.20–7.60 (m, 10H, Ar─H + NH).
27	3378, 3299 (NH_2), 3063 (CH-arom), 1612 (C═N).	5.46 (s, 2H, NH_2), 6.40–7.14 (m, 7H, Ar─H + NH).

aqueous solution of sodium nitrite (0.01 mol) was then added. The diazonium salt thus obtained was filtered into a cold mixture of sodium acetate (2 g) and **4** (0.01 mol) in ethanol (30 mL). The resulting solid was washed with water and recrystallized from the proper solvent to give **6**.

4-(2-Benzothiazolyl)-2-(4-chlorophenyl)-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (7)

A mixture of compound **6a** (0.01 mol) and carbon disulfide (0.012 mol) in pyridine (10 mL) was refluxed for 2 h, then allowed to cool, and poured into cold water (30 mL) and acidified with HCl. The solid product was collected and recrystallized from the proper solvent to give **7**.

4-(2-Benzothiazolyl)-2-(4-chlorophenyl)-3-(*N,N*-dimethylamino)-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (8)

A mixture of compound **6a** (0.01 mol) and dimethylformamide-dimethylacetal (0.01 mol) in *m*-xylene (30 mL) was refluxed for 1 h, then allowed to cool and poured into ether (50 mL). The solid product was collected and recrystallized from the proper solvent to give **8**.

6-Amino-1-(2-benzothiazolyl)-4-methylsulfanyl-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (11)

A mixture of compound **4** (0.01 mol), ketene dithioacetal **9** (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux until the evolution of methyl mercaptan had stopped. After cooling, the reaction mixture was poured into cold water (40 mL) and acidified with HCl. The product was collected by filtration and recrystallized from the proper solvent to give **11**.

6-Amino-1-(2-benzothiazolyl)-4-methyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (14)

A mixture of compound **4** (0.01 mol), 3-aminocrotononitrile **12** (0.01 mol) and triethylamine (0.01 mol) in ethanol (30 mL) was heated under reflux for 0.5 h, then allowed to cool and poured into cold water (50 mL). The solid product was collected and recrystallized from the proper solvent to give **14**.

3-(2-Benzothiazolyl)carboxamide-6-phenyl-4-(4-substituted phenyl)-2-oxo-1,2-dihydropyridines (17a,b)—General Procedure

A mixture of compound **4** (0.01 mol), α,β-unsaturated ketone **15** (0.01 mol) and piperidine (0.05 mol) in ethanol (30 mL) was heated under

reflux for 12 h, the solid product produced on heating was collected and recrystallized from the proper solvent to give **17**.

6-Amino-5-(2-benzothiazolyl)carboxamide-4-(4-methylphenyl) -2-thioxo-1,2-dihydropyridine-3-carbonitrile (20)

A mixture of compound **18** (0.01 mol), cyanothioacetamide **19a** (0.01 mol) and triethylamine (0.01 mol) in ethanol (30 mL) was heated under reflux for 1 h, the solid product produced on heating was collected and recrystallized from the proper solvent to give **20**.

1,6-Diamino-5-(2-benzothiazolyl)carboxamide-4-(4-methyl-phenyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (21)

A mixture of compound **18** (0.01 mol), cyanoacetic acid hydrazide **19b** (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 0.5 h, the solid product produced on heating was collected and recrystallized for the proper solvent to give **21**.

4,6-Dimethyl-1-(2-benzothiazolyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (23)

A mixture of compound **4** (0.01 mol) and acetylacetone (0.01 mol) was heated at 200°C for ten minutes. The reaction mixture was left to cool, then triturated with ethanol. The solid product so formed was collected by filtration and recrystallized from the proper solvent to give **23**.

3-(2-Benzothiazolyl)carboxamide-2*H*-1-benzopyran-2-imine (24)

A mixture of compound **4** (0.01 mol), salicylaldehyde (0.01 mol) and ammonium acetate (0.02 mol) in ethanol (30 mL) was refluxed for 1 h, then allowed to cool. The solid product was collected and recrystallized from the proper solvent to give **24**.

3-(2-Benzothiazolyl)carboxamide-2-oxo-2*H*-1-benzopyran (25)

Method A

A mixture of compound **4** (0.01 mol), salicylaldehyde (0.01 mol) and sodium acetate (2 g) in acetic anhydride (10 mL) was refluxed for 1 h, then allowed to cool. The solid product was collected and recrystallized from the proper solvent to give **25**.

Method B

To a solution of compound **24** (0.01 mol) in boiling ethanol (30 mL), conc. HCl (3 mL) was added. The reaction mixture was allowed to cool down to ambient temperature overnight. The product was collected, washed with cold water and recrystallized from the proper solvent to give **25**.

3-Amino-5-(2-benzothiazolyl)amino-1*H*-pyrazole (27)

A mixture of compound **4** (0.01 mol) and hydrazine hydrate (0.02 mol) was heated at 180°C for 30 minutes. The reaction mixture was left to cool, then triturated with ethanol. The solid product, so formed, was collected by filtration and recrystallized from the proper solvent to give **27**.

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