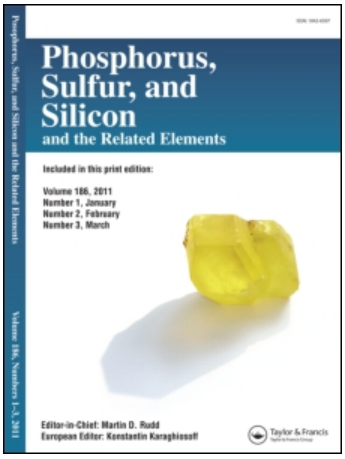

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Cyanoacetanilides Intermediates in Heterocyclic Synthesis. Part 4: Preparation of Some Hitherto Unknown Thiazolidine and Bisthiazolidine Derivatives

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Cyanoacetanilides Intermediates in Heterocyclic Synthesis. Part 4: Preparation of Some Hitherto Unknown Thiazolidine and Bisthiazolidine Derivatives

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*Some novel thiazolidine and bisthiazolidine derivatives were synthesized from the reaction of cyanoacetanilide derivative (**2**) with isothiocyanates in the presence of potassium hydroxide followed by in situ heterocyclization of the resulting adducts with various α-halogenated reagents.*

Keywords Bisthiazolidine; thiazolidine; thiophene derivatives

INTRODUCTION

Many thiazolidine derivatives have been demonstrated to possess antibacterial,[1]antifungal,[2] anticonvulsant,[3] anticancer,[4] and antituberculosis[5] activities. In addition, thiazolidines have reported as novel inhibitors of the bacterial enzyme Mur B that was a precursor acting during the biosynthesis of peptidoglycan.[6] Furthermore, antibacterial,[7] antifungal,[8] insulin releasing,[9] carbonic anhydrase inhibitory,[10] antiinflammtory,[11] and antitumor[12] properties of sulfamoyl moiety were described. In view of the above observations and in continuation of our research program on the chemistry of cyanoacetanilide derivatives,[13–15] we report herein the synthesis of the versatile hitherto unknown thiazolidine and bisthiazolidine derivatives having an sulfamoyl moiety from the readily accessible cyano-acetanilide derivative (**2**).

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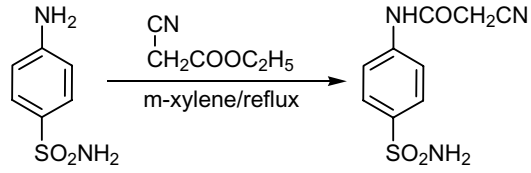
Dedicated to Professor A. M. Sh. El-Sharief on the occasion of his 60th birthday.
Address correspondence to M. S. A. El-Gaby, Chemistry Department, Faculty of Science, Al-Azhar University at Assiut, Assiut 71524, Egypt. E-mail: m_elgaby@hotmail.com

RESULTS AND DISCUSSION

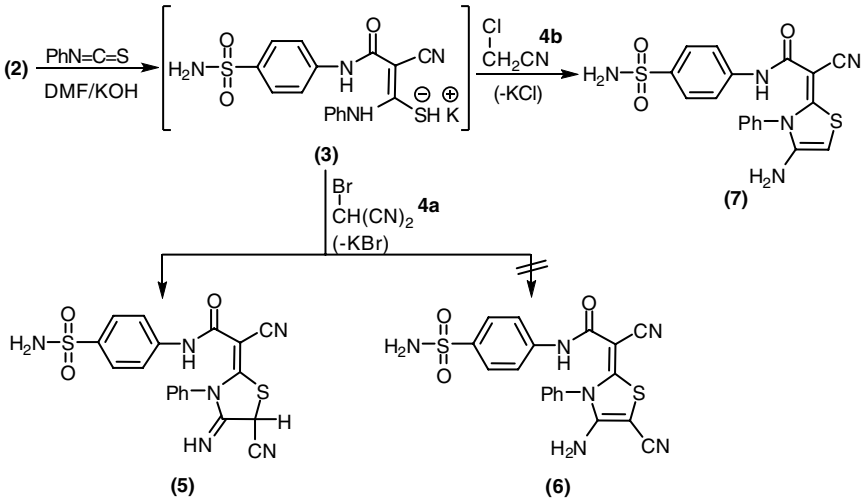
In the present contribution, we investigated the reaction of cyanoacetanilide derivative (**2**) with isothiocyanates in the presence of potassium hydroxide followed by in situ heterocyclization of the resulting adducts with various α-halogenated compounds. The required starting material cyanoaceto-4-sulfamoylanilide (**2**) was synthesized in good yield (92%) through the reaction of sulfanilamide (**1**) with ethyl cyanoacetate in refluxing *m*-xylene (Scheme 1).



(1) **(2)**

SCHEME 1

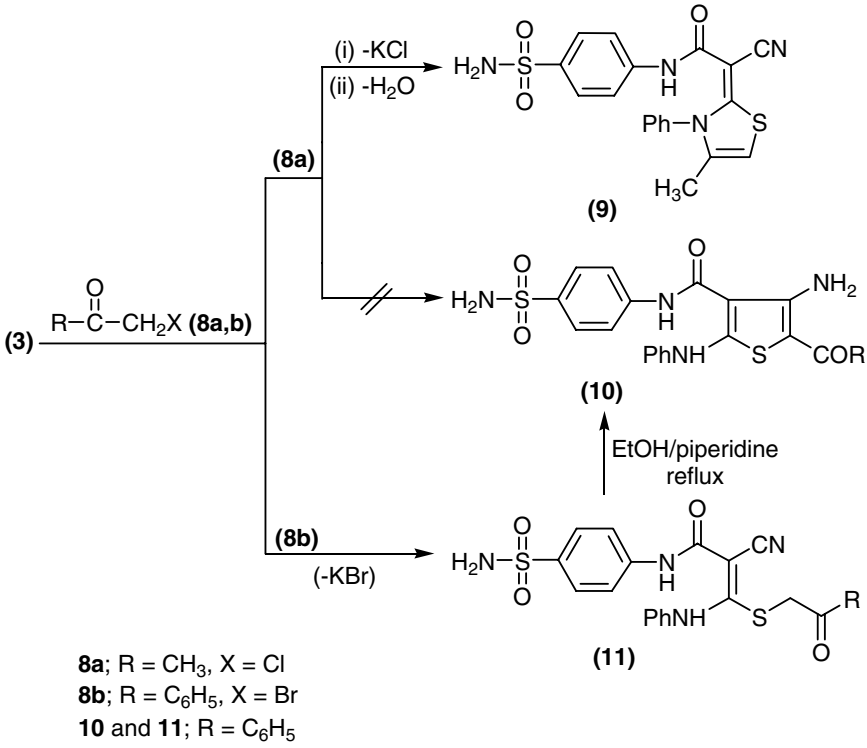
The non-isolable potassium sulfide salt (**3**) was achieved by the nucleophilic addition of active methylene group in compound (**2**) to phenyl isothiocyanate in dry dimethylformamide at room temperature in the presence of potassium hydroxide (Scheme 2). The potassium salt (**3**) was exploited to synthesize some new thiazolidine derivatives. Treatment of intermediate (**3**) with bromomalononitrile (**4a**) at room temperature



SCHEME 2

gave iminothiazolidine derivative **5** in high yield (86%). The structure of the isolated product was confirmed based on elemental analysis and spectral data. Its infrared spectrum showed a strong absorption band at 2194 cm^{-1} due to C≡N group in addition to the absorption bands characteristic for NH and C=O (amide) functional groups. Structure (**6**) was ruled out based on the ^{1}HNMR spectrum of the reaction product, which revealed a signal a δ 7.27 ppm for a methine proton in addition to the presence of two NH and aromatic protons. Formation of (**5**) was assumed to proceed via the initial alkylation followed by in situ heterocyclization[16] through nucleophilic addition of the secondary amino group to one of the two cyano groups. Cycloalkylation of the intermediate (**3**) with chloroaceto-nitrile (**4b**) afforded the novel aminothiazolidine derivative (**7**) in acceptable yield (72%). The molecular structure of (**7**) was established based on analytical and spectral data. Its ^{1}HNMR spectrum in DMSO-d_6 was characteristic by the presence of a singlet at δ 6.90 ppm due to the thiazole-H. The reaction mechanism was assumed to proceed through initial alkylation followed by the addition of the secondary amino group to the cyano group and tautomerization to yield the cyclized product (**7**), (Scheme 2).

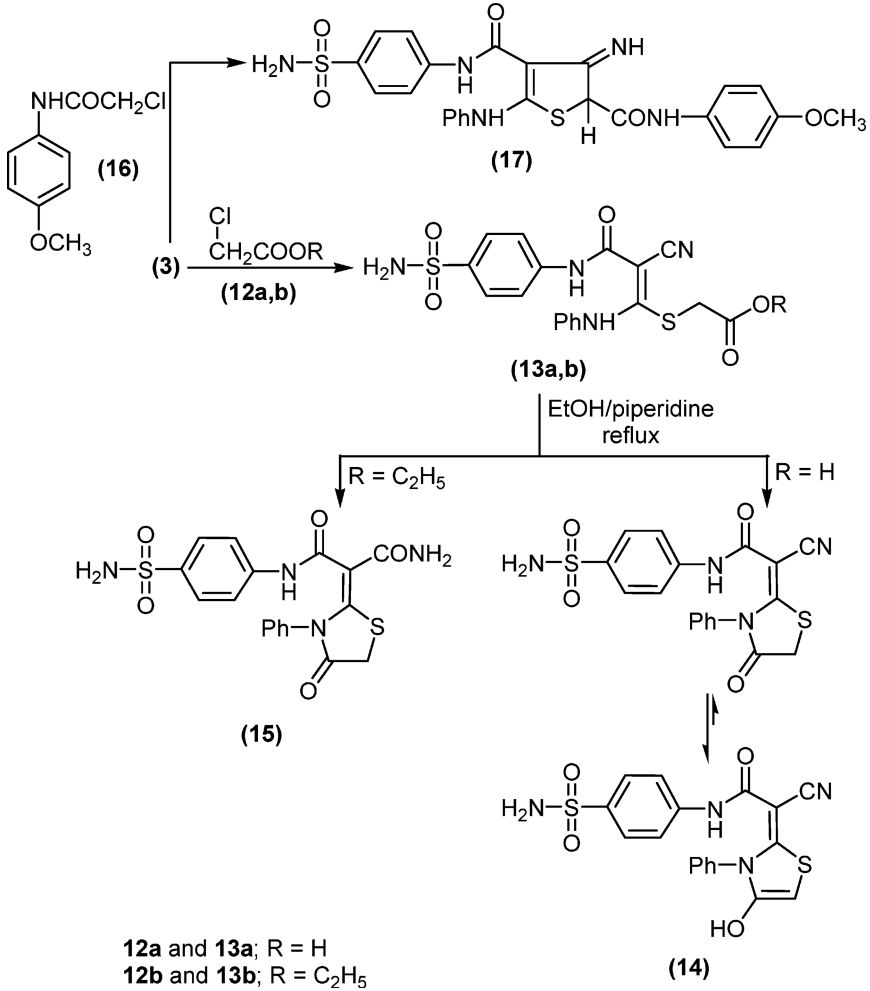
Cyclocondensation of the intermediate salt (**3**) with chloroacetone (**8a**) at room temperature afforded the corresponding 2,3-dihydrothiazole derivative (**9**). The other possible structure (**10**; R = CH_3) was ruled out based on elemental analysis and spectral data. The infrared spectrum of compound (**9**) showed the characteristic absorption band at 2170 cm^{-1} for the C≡N functional group. The mass spectrum of compound (**9**; $C_{19}H_{16}N_4O_3S_2$) showed a molecular ion peak at m/z = 412 and the base peak was found in the spectrum at m/z = 214. The structure (**9**) resulting from the initial alkylation followed by intramolecular cyclization through dehydration to form (**9**). On the other hand, treatment of (**3**) with phenacyl bromide (**8b**) gave the thioether derivative (**11**; R = C_6H_5), by elimination of potassium bromide. The structure of thioether (**11**) was confirmed by examining spectral data. Its infrared spectrum indicated the presence of the C≡N and C=O absorption bands. In addition the structure (**11**) was supported by ^{1}HNMR spectrum which revealed a singlet at δ = 4.01 ppm assigned to the methylene moiety. Cyclization of (**11**) by refluxing in ethanol in the presence of piperidine gave the novel aminothiophene derivative (**10**; R = C_6H_5), via Thorpe-Ziegler reaction.[17] the structure of compound (**10**; R = C_6H_5) was confirmed by its infrared spectrum which indicated the absence of C≡N absorption band and contain the characteristic absorption bands for NH_2 and C=O functional groups. The formation of compound (**10**) was assumed to proceed via nucleophilic attack of active methylene to the cyano group and tautomerization[17] (Scheme 3).



SCHEME 3

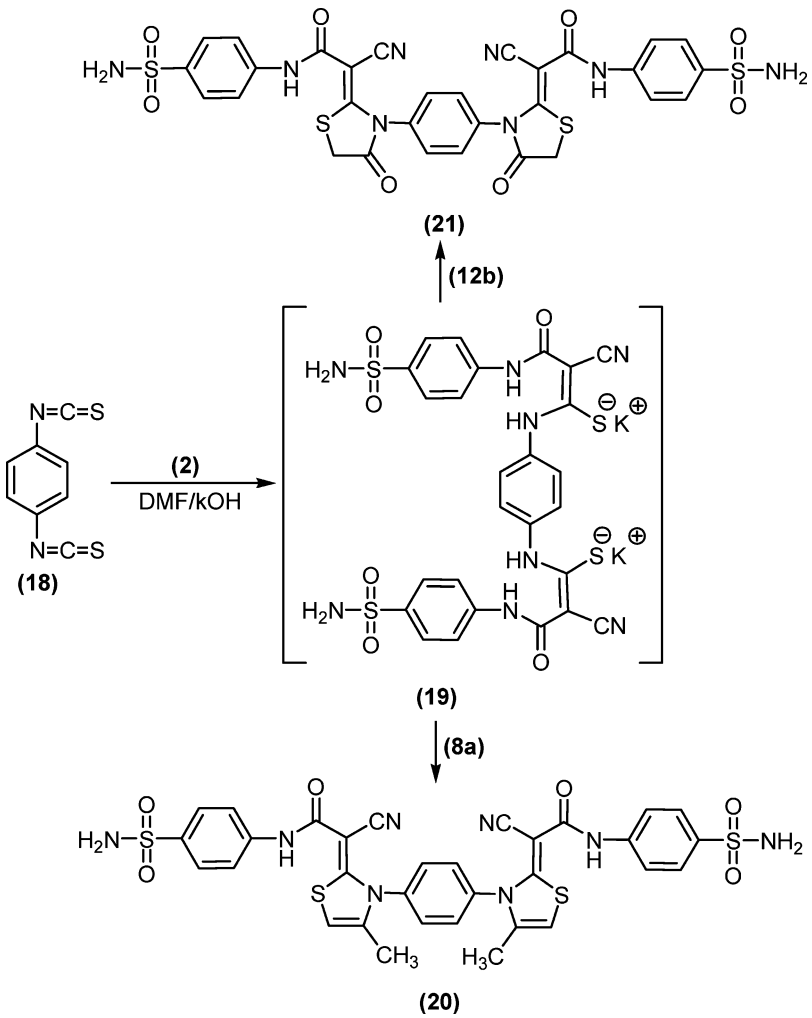
Our investigation was also extended to study the reaction of intermediate salt (**3**) with chloroacetic acids (**12a**,**b**). thus, the reaction of (**3**) with α-chloroacetic acid (**12a**) and ethyl chloroacetate (**12b**) at room temperature gave the acyclic products (**13a**) and (**13b**), respectively; via loss of potassium chloride. The infrared spectra of compounds (**13a**,**b**) indicated the presence of the C≡N and C═O functional groups. Thiazolidine derivative (**14**) was obtained by cyclization of (**13a**) in refluxing ethanol in the presence of piperidine, through dehydration of water. In the mass spectrum of compound (**14**; $C_{18}H_{14}N_4O_4S_2$) a molecular ion peak was found at m/z = 414 (23.20), and the base peak was observed in the spectrum at m/z = 215. On the other hand, refluxing of (**13b**) in ethanolic solution containing a few drops of piperidine as basic catalyst afforded the novel thiazolidinone (**15**), through elimination of ethanol with partial hydrolysis of cyano group. When intermediate salt (**3**) was treated with *N*-(4-methoxy-phenyl)chloroacetamide (**16**) at room temperature, thiophene derivative (**17**) was formed smoothly. The structure

of compound (**17**) was confirmed by its infrared spectrum, which exhibited the disappearance of absorption band for C≡N group. Compound (**17**) was assumed to be formed via initial alkylation followed by intramolecular cyclization through Thorpe-Ziegler reaction[17] (Scheme 4).



SCHEME 4

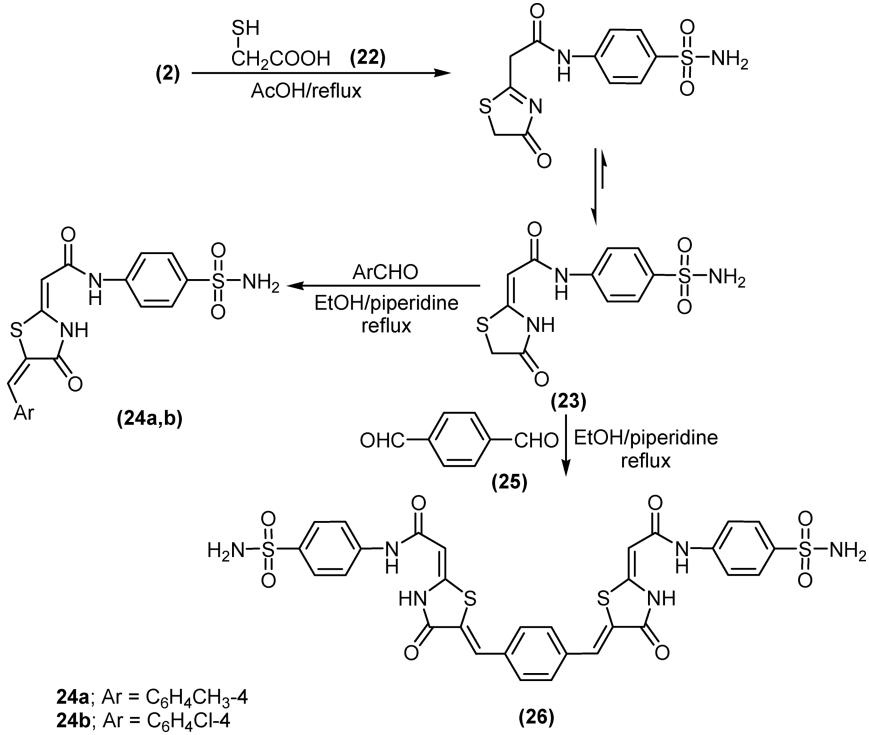
The present contribution was extended to synthesize hitherto unknown bisthiazolidinone derivatives from 1,4-phenylenediisothiocyanate (**18**) and cyanoacetanilide (**2**). The reaction of 1,4-phenylenediisothiocyanate (**18**) with cyanoacetanilide in the presence of potassium hydroxide at room temperature gave the non-isolated adduct (**19**)



SCHEME 5

(Scheme 5). The latter was converted into bisthiazolidinone derivative (**20**) by treatment with chloroacetone (**8a**) at room temperature, through initial alkylation and elimination of water. Also, cyclization of the adduct (**19**) with ethyl chloroacetate (**12b**) afforded the corresponding bis(thiazolidinone) derivative (**21**), via initial alkylation and elimination of ethanol. The mass spectrum of compound (**20**) exhibited a molecular ion peak at m/z = 750 (3.23%) corresponding to the molecular formula $C_{30}H_{22}N_8O_8S_4$ with base peak at m/z = 63.

Refluxing of cyanoacetanilide derivative (**2**) with sulfanylacetic acid (**22**) in glacial acetic acid furnished thiazolidinone derivative (**23**) based on its analytical and spectral data. Its infrared spectrum revealed characteristic absorption band for C=O (thiazolidinone) functional group. The ^{1}H NMR spectrum of the reaction product recorded in DMSO-d_6 displayed a signal at $\delta = 5.85$ ppm for a methylidene-H in addition to the presence of methylene, two NH, NH_2 and aromatic protons. Formation of thiazolidinone (**23**) is assumed to proceed via initial nucleophilic addition of mercapto group to cyano group followed by intramolecular cyclization through elimination of water to yield (**23**). Condensation of compound (**23**) with aromatic aldehyde in refluxing ethanol in the presence of piperidine yielded the novel 5-arylmethylidene-2-[*N*-(4-sulfamoylphenyl)acteamide-2-yl]-4,5-dihydro-4-thiazolidinones (**24a,b**). Bisthiazolidinone derivative (**26**) was achieved by refluxing of compound (**23**) with terephthalaldehyde (**25**) in ethanol at reflux temperature in the presence of piperidine (Scheme 6).



SCHEME 6

CONCLUSIONS

In conclusion, the non-isolable intermediate (**3**) was exploited to synthesize some novel thiazolidine derivatives via its reaction with α-halo compounds. In addition, bisthiazolidine derivatives were prepared by various methods.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}H NMR spectra were obtained in DMSO on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GCMS\QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center, Faculty of Science (Cairo University, Egypt). The characteristics data for prepared compounds are given in Table I. Also the spectral data are collected in Table II.

Preparation of Cyanoaceto-4-sulfamoylanilide (2)

A mixture of sulfanilamide **1** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in *m*-xylene (30 mL) was refluxed for 4 h, the solid product which produced on heating was collected and crystallized from dioxane as colorless crystals, m.p. 230°C (lit. m.p. 228°C).[18]

Preparation of Compounds (5) (R = CN), (7), (9), (11), (13a; R = H), (13b; R = C_2H_5), (17), (20), and (21)—General Procedure

To suspension of finely powdered potassium hydroxide (0.01 mol) in dry dimethylformamide (10 mL) at 0°C the anilide (**2**, 0.01 mol) and then the isothiocyanate (0.01 mol) were added in portions. The reaction mixture was stirred at room temperature for 3 h and then treated with α-halogenated compound (0.01 mol) and left at room temperature for 24 h; then it was poured into ice/water and acidified with 0.1 N HCl at pH 3-4. The resulting precipitate was filtered off, dried, and recrystallized from the proper solvent.

Formation of Compounds 10, 14, and 15—General Procedure

A mixture of compound 11, 13a, or 13b (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 1 h, the solid

TABLE I Characteristics Data for the Synthesized Compounds

Compd. no.	Yield (%)	Solvent cryst.	M.p. (°C)	Molecular formula (mol. wt.)	Elemental analyses calcd./found (%)		
					C%	H%	N%
5	86	Benzene	230–232	$C_{19}H_{14}N_6O_3S_2$ (438)	52.05 52.10	3.19 3.10	19.17 19.10
7	72	Benzene	240–241	$C_{18}H_{15}N_5O_3S_2$ (413)	52.30 52.25	3.63 3.70	16.94 16.90
9	60	AcOH	260–262	$C_{19}H_{16}N_4O_3S_2$ (412)	55.23 55.10	3.88 3.80	13.59 13.50
10	65	AcOH	>300	$C_{24}H_{20}N_4O_4S_2$ (492)	58.53 58.40	4.06 4.00	11.38 11.30
11	75	Benzene	190–191	$C_{24}H_{20}N_4O_4S_2$ (492)	58.53 58.40	4.06 4.00	11.38 11.30
13a	75	Benzene	150–152	$C_{18}H_{16}N_4O_5S_2$ (432)	50.00 50.10	3.70 3.80	13.96 12.90
13b	80	Benzene	90–91	$C_{20}H_{20}N_4O_5S_2$ (460)	52.17 52.20	4.34 4.30	12.17 12.10
14	63	AcOH	230–231	$C_{18}H_{14}N_4O_4S_2$ (414)	52.17 52.10	3.38 3.30	13.52 13.60
15	50	AcOH	70–72	$C_{18}H_{16}N_4O_5S_2$ (432)	50.00 50.00	3.70 3.60	12.96 12.90
17	70	AcOH	260–261	$C_{25}H_{23}N_5O_5S_2$ (537)	55.86 55.70	4.28 4.20	13.03 13.10
20	60	EtOH/DMF	250–251	$C_{30}H_{22}N_8O_8S_4$ (750)	48.00 48.10	2.93 2.90	14.93 15.00
21	70	EtOH/DMF	>300	$C_{32}H_{26}N_8O_6S_4$ (746)	51.47 51.40	3.48 3.40	15.01 15.10
23	80	AcOH	240–241	$C_{11}H_{11}N_3O_4S_2$ (313)	42.17 42.10	3.51 3.40	13.41 13.30
24a	50	AcOH	250–251	$C_{19}H_{17}N_3O_4S_2$ (415)	54.93 54.80	4.09 4.10	10.12 10.12
24b	60	AcOH	278–279	$C_{18}H_{14}ClN_3O_4S_2$ (435.5)	49.39 49.20	3.21 3.10	9.64 9.50
26	70	EtOH/DMF	>300	$C_{30}H_{24}N_6O_8S_4$ (724)	49.72 49.60	3.31 3.20	11.60 11.70

product which produced on heating was collected and recrystallized from the proper solvent to give **10**, **14**, and **15**, respectively.

Synthesis of 2-[N-(sulfamoylphenyl)acetamide-2-yl]-4,5-dihydro-4-thiazolidinone (23)

A mixture of compound **2** (0.01 mol) and sulfanylacetic acid **22** (0.01 mol) in glacial acetic acid (10 mL) was heated under reflux for 3 h, then allowed to cool and poured into water (50 mL). The solid product was collected and recrystallized to give **23**.

TABLE II Spectral Data of the Synthesized Compounds

	IR/ν_{max} (cm^{-1})	^1H NMR (DMSO-d_6) (δ/ppm)
5	3336, 3262 (NH_2), 2194 (C≡N), 1656 (C═O; amide).	6.50 (s, 2H, SO_2NH_2; exchangeable), 7.01 (s, 1H, thiazole-H), 7.27–7.75 (m, 10H, Ar-H + NH), 10.2 (s, 1H, NH; exchangeable).
7	3351, 3229 (NH_2), 1645 (C═O; amide).	6.60 (s, 2H, NH_2; exchangeable), 6.90 (s, 1H, thiazole-H), 7.26–7.78 (m, 11H, Ar-H+ NH_2), 9.80 (s, 1H, NH; exchangeable).
9	3400, 3284 (NH_2), 2170 (C≡N), 1624 (C═O; amide).	1.87 (s, 3H, CH_3), 6.99 (s, 1H, thiazole-H), 7.23 (s, 2H, SO_2NH_2; exchangeable), 7.52–7.77 (m, 9H, Ar-H), 9.08 (s, H, NH; exchangeable).
10	3416, 3342, 3264 (NH/NH_2), 1662 (C═O; benzoyl).	7.16-7.81 (m, 16H, Ar-H+NH_2), 8.16, 8.40 (2s, 2H, 2NH; exchangeable), 9.45 (2H, NH_2; exchangeable).
11	3280, 3256 (NH_2), 2198 (C≡N), 1686 (C═O; amide), 1656 (C═O; benzoyl)..	4.01 (s, 2H, SCH_2), 7.22–8.03 (m, 16H, Ar-H + NH_2), 9.85, 10.21 (2s, 2H, 2NH; exchangeable).
13a	3432 (OH), 2190 (C≡N), 1720 (C═O).	4.1 (s, 2H, SCH_2), 7.39-7.80 (m, 11H, Ar-H + SO_2NH_2), 9.79, 10.67 (2s, 2H, 2NH; exchange-able), 11.97 (s, H, OH; exchangeable).
13b	3300, 3256 (NH_2), 2926 (CH-aliph.), 2198 (C≡N), 1734 (C═O; ester), 1654 (C═O; amide).	1.20 (t, 3H, CH_3), 2.90 (s, 2H, SCH_2), 4.21 (q, 2H, CH_2), 7.29–7.96 (m, 11H, Ar-H + SO_2NH_2), 9.7, 10.11 (2s, 2H, 2NH; exchangeable).
14	3384, 3278 (NH_2), 2190 (C≡N), 1718 (C═O; thiazolidinone), 1660 (C═O; amide).	6.05 (s, 1H, thiazolidinone-H), 7.21 (s, 2H, SO_2NH_2; exchangeable), 7.67–7.79 (m, 9H, Ar-H), 10.49 (s, 1H, NH; exchangeable), 12.30 (s, 1H, OH; exchangeable).
15	3440, 3338 (NH_2), 1648 (C═O; amide).	3.65 (s, 2H, NH_2; exchangeable), 4.01 (s, 2H, SCH_2), 6.75 (s, 2H, NH_2; exchangeable), 7.21–7.79 (m, 9H, Ar-H), 12.2 (s, 1H, NH; exchangeable),
17	3402, 3260 (NH_2), 2928 (CH-aliph.), 1664 (C═O; amide).	3.73 (s, 3H, OCH_3), 5.11 (s, 1H, thiophene-H), 6.90–7.79 (m, 15H, Ar-H+ NH_2), 8.92, 9.35, 10.26, 12.21 (4s, 4H, 4NH; exchangeable),
20	3330, 3256 (NH_2), 2198 (C≡N), 1734 (C═O; ester), 1684 (C═O; amide).	4.02, 4.17 (2s, 4H, $2SCH_2$), 7.28–7.79 (m, 16H, Ar-H + $2SO_2NH_2$), 9.78, 10.26 (2s, 2H, 2NH; exchangeable),
21	3346, 3108 (NH_2), 2182 (C≡N), 1640 (C═O; amide).	2.03 (s, 6H, $2CH_3$), 7.02 (s, 2H, thiazolidine), 7.22 (s, 4H, $2SO_2NH_2$; exchangeable), 7.72–7.84 (m, 12H, Ar-H), 9.12 (s, 2H, 2NH; exchangeable).
23	3320, 3180, 3110 (NH/ NH_2), 1708 (C═O; thiazolidinone), 1660 (C═O; amide).	3.74 (s, 2H, SCH_2), 5.85 (s, 1H, methylidene-H), 7.23 (s, 2H, SO_2NH_2; exchangeable), 7.76 (m, 4H, Ar-H), 10.18, 11.83 (2s, 2H, 2NH; exchangeable).

(Continued on next page)

TABLE II Spectral Data of the Synthesized Compounds *(Continued)*

	IR/ν_{max} (cm^{-1})	^{1}H NMR (DMSO-d_6) (δ/ppm)
24a	3344, 3252 (NH_2), 1684 (C═O; thiazolidinone), 1640 (C═O; amide).	2.09 (s, 3H, CH_3), 6.03 (s, 1H, methylidene-H), 7.25-7.84 (m, 11H, Ar-H + SO_2NH_2+ methylidene-H), 10.40, 12.24 (2s, 2H, 2NH; exchangeable).
24b	3332, 3240 (NH_2), 1686 (C═O; thiazolidinone), 1660 (C═O; amide).	6.05 (s, 1H, methylidene-H), 7.25 (s, 2H, SO_2NH_2; exchangeable), 7.51–7.79 (m, 9H, Ar-H + benzylidene-H), 10.47, 12.30 (2s, 2H, 2NH; exchangeable).
26	3436, 3400 (NH_2), 1686 (C═O; thiazolidinone), 1654 (C═O; amide).	6.10 (s, 2H, methylidene-H), 7.20–2.8 (m, 18H, Ar-H + 2SO_2NH_2+ benzylidene-H), 10.1, 10.42 (2s, 2H, 2NH; exchangeable).

Formation of Compounds (24a,b) and 26—General Procedure

A mixture of compound **23** (0.01 mol), aromatic aldehyde or terephthalaldehyde **25** (0.01 mol) and piperidine (0.01 mol) in ethanol (40 mL) was heated under reflux for 3 h, the solid product, which was produced on heating, was collected and recrystallized to give **24a**,**b** and **26**, respectively.

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