Ethyl {4-[2-(Saccharin-2-yl)acetylsulfamoyl]phenylazo}cyanoacetate in the Synthesis of Polyfunctionally Heteroaromatic Derivatives

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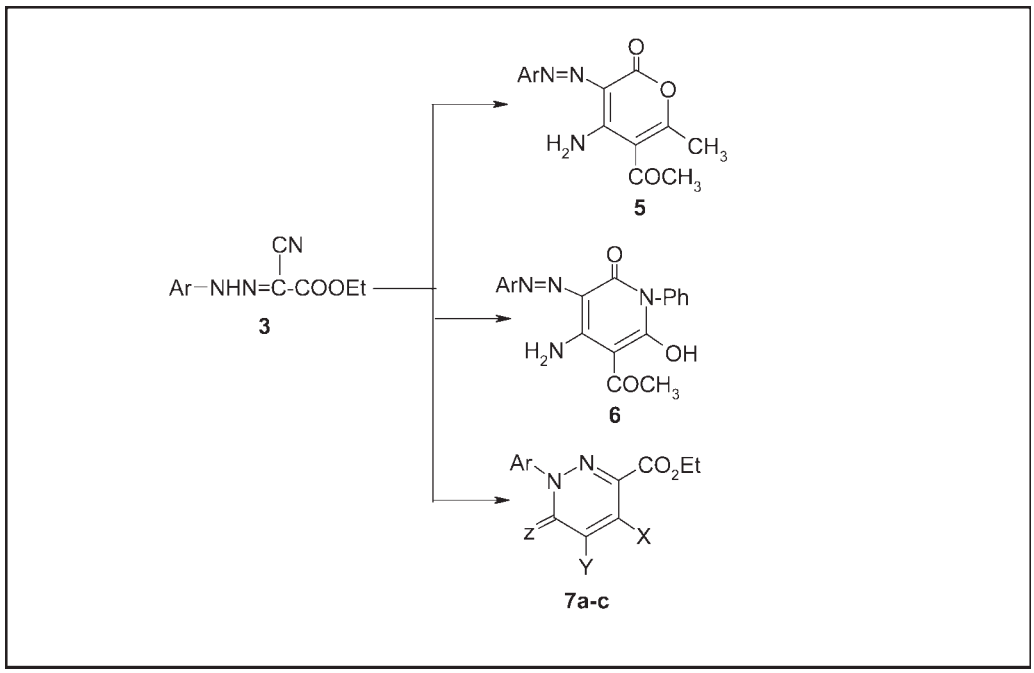

An efficient and direct one-pot reaction of ethyl saccharinylcyanoacetate derivative **3** with a variety of active methylene reagents and nitrogen nucleophiles afforded novel series of polyfunctionally substituted heteroaromatic derivatives **5–13**, respectively. The pyrazole derivative **13** was seemed to be the excellent precursors for the synthesis of pyrazolo[1,5-a]pyrimidine derivatives **14–24**. The antimicrobial screening of some synthesized products was evaluated against some selected bacteria and fungi. The structures of the synthesized derivatives were established by elemental and spectral data.

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INTRODUCTION

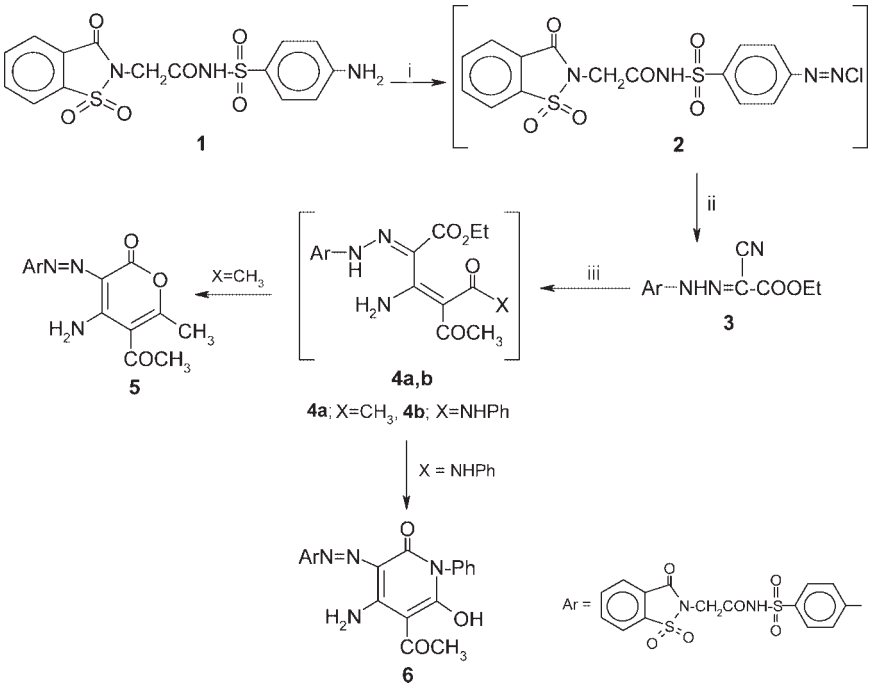
The increasing medicinal potential of both saccharine and sulfonamide derivatives as intermediate to biologically active compounds [1–5] and in continuation of our efforts [6,7] in the synthesis of heterocyclic systems incorporating saccharinyl and sulfonamide moieties as potential pharmaceuticals. We reported here on the utility of ethyl saccharinylcyanoacetate **3** as building blocks for synthesis of new polyfunctionally substituted heteroaromatic derivatives of pyran, pyridine, pyridazine, triazine, pyrimidine, and their analogues of sulfonamido moiety of promising therapeutic applications [8–13].

RESULTS AND DISCUSSION

The key starting material ethyl {4-[2-(saccharin-2-yl)-acetylsulfamoyl]phenylazo}cyanoacetate (**3**) was prepared by diazotization of the sulfanilamide derivative **1** followed by coupling the resulting intermediate **2** with ethyl cyanoacetate in ethanolic sodium acetate solution at 0–5°C. The structure of compound **3** was established on the basis of its elemental analysis and spectral data. Thus, its IR spectrum showed bands at 3320 and 3290 cm^{-1} for νNH groups, 2220 cm^{-1} for νCN, and at 1725, 1680 cm^{-1} for carbonyl groups. The ^1H NMR spectrum showed signals as triplet at $\delta = 1.53$ for methyl proton, quartet at 4.50, singlet at $\delta = 4.85$ for two methylene protons, multiplets at $\delta = 7.21$–8.35 for aromatic protons and two singlet at $\delta = 8.53$, 9.01 for 2NH protons, which disappeared upon addition of D_2O to the NMR sample (Scheme 1).

The reactivity of compound **3** toward 1,3-dicarbonyl compounds was investigated with respect to the synthesis of highly substituted pyran and pyridine. Thus, the reaction of equimolar amounts of compound **3** and acetylacetone and/or acetoacetanilide derivative in refluxing

Scheme 1. (i) $NaNO_2$/AcOH/HCl; (ii) $NCCH_2COOEt$, AcONa; (iii) $CH_3COCH_2COCH_3$ or $CH_3COCH_2CONHPh$, dioxane, Et_3N.



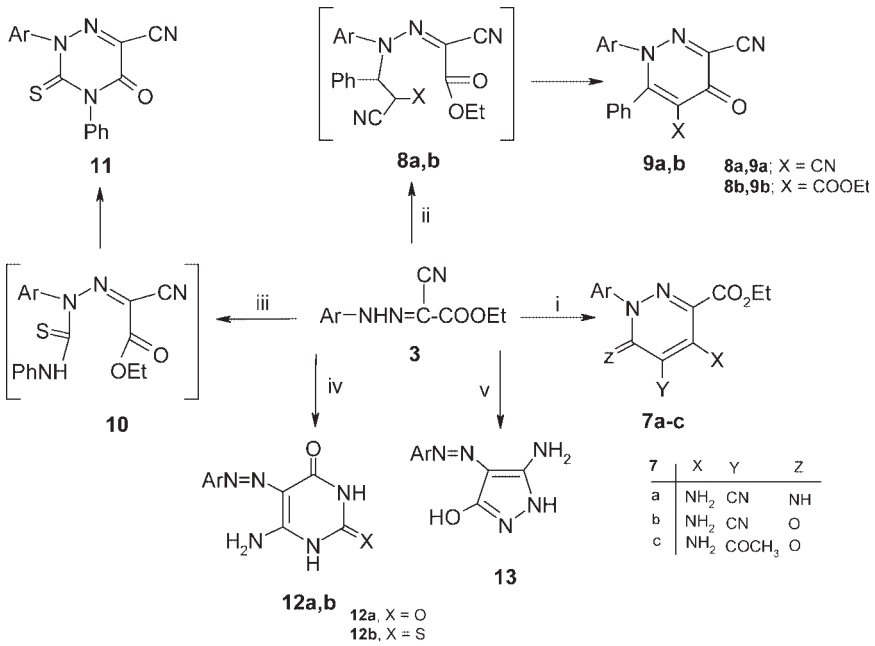
1,4-dioxane containing a few drops of triethylamine afforded 4-(5-acetyl-4-amino-6-methyl-2-oxo-2*H*-pyran-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**5**) and 4-(5-acetyl-4-amino-6-hydroxy-2-oxo-1-phenyl-1,2-dihydropyridin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]-benzenesulfonamide (**6**), respectively. In a similar manner, the treatment of compound **3** with malononitrile or ethyl cyanoacetate and/or ethyl acetoacetate afforded the pyridazine derivatives **7a–c**, respectively (Scheme 2). Moreover, the reaction of compound **3** with 2-benzylidenemalononitrile and/or ethyl 2-cyano-3-phenylacrylate in refluxing 1,4-dioxane containing a few drops of triethylamine yielded the pyridazine derivatives **9a,b**.

The formation of compounds **9a,b** are assumed to proceed *via* Michael-type addition of the NH of the hydrazone moiety in **3** to the activated α,β-unsaturated center of substituted cinnamonitriles, yielding a cyclic Michael adducts **8a,b**, which are cyclized followed by the aromatization to the final products **9a,b** *via* elimination of an ethanol molecule and subsequent dehydrocyanation. The reaction of compound **3** with phenyl isothiocyanate afforded 4-(6-cyano-5-oxo-4-phenyl-3-thioxo-4,5-dihydro-3*H*-[1,2,4]triazin-2-yl)-*N*-[2-(saccharin-2-yl)-acetyl]benzenesulfonamide(**11**). Compound **11** was assumed to be formed *via* an initial nucleophilic attack of NH group of compound **3** on the isothiocyanate moiety giving the adduct **10**, which cyclized *via* the elimination of ethanol molecule to give compound **11**. The structure of compound **11** was assigned on the basis of their elemental analysis and spectral data. Its IR spectrum showed bands at 3290 cm^{-1} for νNH, 2215 cm^{-1} for νCN, and 1685–1675 cm^{-1} for νCO.

As an extension of such synthetic route, the behavior of hydrazonoester **3** toward some nitrogen nucleophiles was investigated with the aim of synthesizing a biologically active substituted pyrimidine and pyrazole derivatives. Thus, the reaction of compound **3** with equimolar amounts of urea or thiourea, in refluxing ethanolic sodium ethoxide solution gave the corresponding pyrimidine derivatives **12a,b**. While the reaction of compound **3** with hydrazine hydrate in refluxing absolute ethanol yielded, 4-(5-amino-3-hydroxy-1*H*-pyrazol-4-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**13**). The structure of compound **13** was assigned on the basis of elemental analysis and spectral data which agree with the proposed structure (Scheme 2). 5-Aminopyrazole **13** has been emphasized as a new synthetic auxiliary used for the preparation of pyrazolo[1,5-a]pyrimidine derivatives [14,15], which associated with a great applications in pharmaceutical fields [16–19] and dyestuff industry [20,21]. Thus, the reaction of compound **13** with acetylacetone in refluxing glacial acetic acid afforded 4-(5,7-dimethyl-2-hydroxypyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**14**). Reaction of compound **13** with aromatic aldehydes *viz* benzaldehyde and 4-methoxybenzaldehyde in absolute ethanol yielded Schiff bases **15a,b,** respectively (Scheme 3).

The study was extended to investigate the behavior of Schiff bases toward some active methylene compounds. Thus, the treatment of **15a,b** with malononitrile afforded

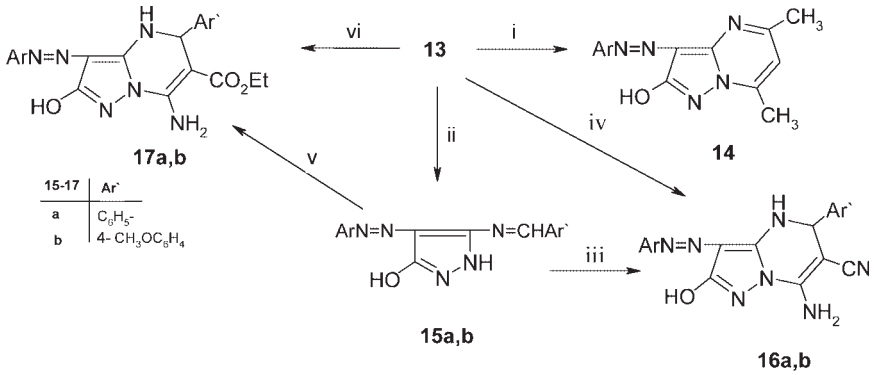
Scheme 2. (i) $NCCH_2CN$ or $NCCH_2CO_2Et$ or $CH_3COCH_2CO_2Et$, dioxane, Et_3N; (ii) $PhCH{=}C(CN)_2$ or $PhCH{=}C(CN)CO_2Et$, dioxane, Et_3N; (iii) PhNCS, dioxane, Et_3N; (iv) H_2NCONH_2 or H_2NCSNH_2, NaOEt; (v) $N_2H_4{\cdot}H_2O$, EtOH.



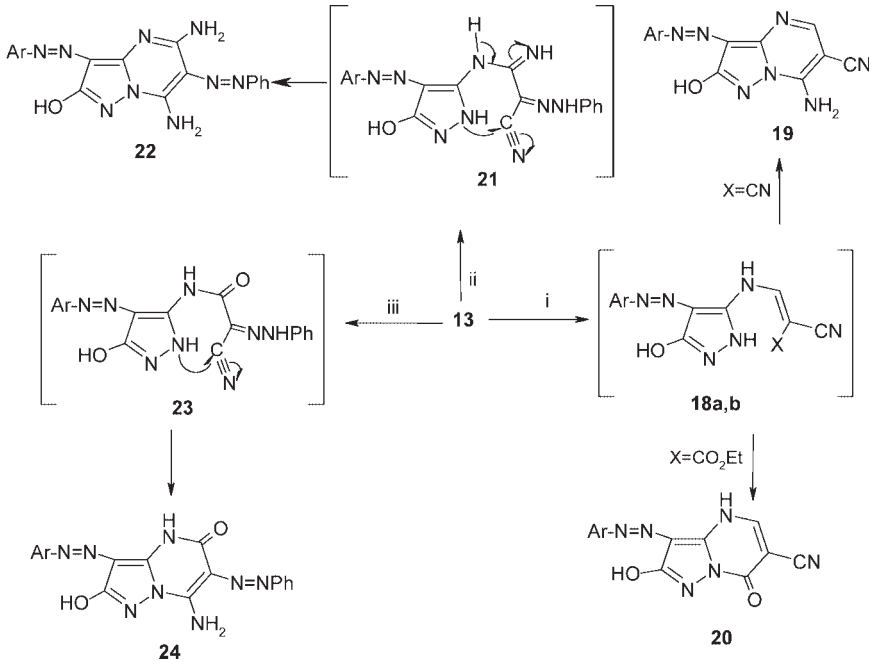
the pyrazolo[1,5-a]pyrimidines **16a,b**, which also obtained authentically, from the reaction of compound **13** with β-aryl-α-cyanoacrylonitrile derivatives in refluxing 1,4-dioxane, which are identical in all respects (m.p., m.m.p., and spectral data). The formation of compounds **16a,b** are assumed to proceed *via* initial addition of the active methylene of malononitrile to the double bond of the Schiff bases **15a,b** to form the non-isolable Michael adduct, which also formed *via* the initial attack of the exocyclic amino group of compound **13** on the activated double bond of acrylonitrile derivatives. This Michael adduct undergoes intramolecular cyclization to give compounds **16a,b**. Additionally, the reaction of Schiff bases **15a,b** with ethyl cyanoacetate yielded pyrazolo[1,5-a]pyrimidines **17a,b** which also obtained *via* independent synthesis from the reaction of compound **13** with β-aryl-α-cyanoacrylate derivatives, which are identical in all respects (m.p., m.m.p., and spectral data) (Scheme 3). Also, the treatment of compound **13** with ethoxymethylenemalononitrile and/or ethyl ethoxymethylenecyanoacetate in refluxing dimethylformamide containing a few drops of piperidine afforded the pyrazolopyrimidine derivatives **19** and **20**, respectively (Scheme 4).

The reaction of compound **13** with 2-phenylhydrazonomalononitrile [22] in refluxing absolute ethanol containing a few drops of pyridine afforded 4-(5,7-diamino-2-hydroxy-6-phenylazopyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-

Scheme 3. (i) $CH_3COCH_2COCH_3$, AcOH; (ii) Ar′CHO, EtOH; (iii) $CH_2(CN)_2$, EtOH, piperidine; (iv) Ar̀CH=C(CN)$_2$, 1,4-dioxane; (v) $NCCH_2CO_2Et$, EtOH, piperidine; (vi) Ar̀CH=C(CN)CO_2Et, 1,4-dioxane.



Scheme 4. (i) EtOCH=C(X)CN, DMF, piperidine; (ii) PhNHN=C(CN)$_2$, EtOH, pyridine; (iii) PhNHN=C(CN)CO$_2$Et, EtOH, pyridine.



[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**22**). The formation of compound **22** was assumed *via* the condensation of the 5-NH_2 group of the pyrazole ring with the cyano group of malononitrile derivative to yield the intermediate **21**, in which internal nucleophilic attack of 1-NH group of the pyrazole ring on the other cyano group followed by a migration of 5-NH proton of the pyrazole ring to the nitrogen atom of imino group to yield the nonisolable adduct, which tautomerized forming the isolable product **22**. While, the reaction of compound **13** with ethyl 2-phenylhydrazonocyanoacetate [23] gave nonisolable intermediate **23**, which cyclized to afford 4-(7-amino-2-hydroxy-5-oxo-6-phenylazo-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (**24**) (Scheme 4). The structures of the synthesized compounds were assigned on the basis of elemental analysis and spectral data (*c.f.*, experimental).

The antimicrobial activity. The antimicrobial activities of some synthesized compounds were screened *in vitro* using the hole plate and filter paper methods [24] for their antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* as gram-negative bacteria and *Staphylococcus aureus* as gram-positive bacteria.

Whereas the antifungal activity was tested against *Aspergillus niger* and *Fusarium oxysporium*. Ampicillin as an antibacterial agent and Clotrimazole as an antifungal were used as a reference drugs to evaluate the potency of the tested compounds under the same conditions. The minimal inhibitory concentration (MIC) values listed in Table 1 show that all the tested compounds have a similar or highest degree of inhibition area against the organisms relative to the reference drugs used.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 298 spectrophotometer.^{1}H and ^{13}C NMR spectra were obtained on an Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70 eV EI mode).

^{13}C NMR values of saccharinylsulfonamide moiety for compounds **5–24** are the same as in compound **3** with δ ± 0.1–0.5 ppm.

Ethyl {4-[2-(saccharin-2-yl)acetylsulfamoyl]phenylazo}-cyanoacetate (3). A cold solution of diazonium chloride **2** (30 mmol) [prepared from the addition of a cold solution of sodium nitrite (0.69 g, 10 mmol) in H_2O (5 mL) to a cold solution of compound **1** (3.95 g, 10 mmol) in concentrated hydrochloric acid (10 mL) and glacial acetic acid (10 mL) at 0–5°C] was added dropwise to a solution of ethyl cyanoacetate (30 mmol) in ethanol (30 mL) containing sodium acetate (5.0 g). After the complete addition of the diazonium chloride, the reaction mixture was stirred at room temperature overnight. The precipitated product which separated upon dilution with cold water (40 mL) was filtered off, washed with water (3 × 30 mL), dried and recrystallized from *n*-butanol to give **3**. Yield, 3.79 g (73%); m.p. 141–143°C; IR: ν = 3320, 3290 (NH), 2220 (CN), 1725, 1680 (CO), 1350, 1130 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$): δ = 1.53 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 4.85 (s, 2H, CH_2), 7.21–8.35 (m, 8H, ArH), 8.53, 9.01 (2s, 2H, 2NH, exchangeable); ^{13}C NMR: δ = 14.5 (CH_3), 36.3

Table 1

In vitro antimicrobial activity of the tested compounds.

	E. coli		*P. aeruginosa*		*S. aureus*		*A. niger*		*F. oxysporium*	
Compound No	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC
5	++	125	++	125	++	250	++	250	++	125
6	++	250	+	125	+++	250	+	250	++	500
7a	+++	500	++	250	++	125	++	250	+	125
9b	+++	125	++	250	+++	500	++	500	++	125
11	++	125	++	125	+	125	++	250	+++	125
12b	++	125	++	250	+++	250	++	125	++	250
13	++	250	++	125	++	125	++	125	+	250
16a	++	125	++	250	++	250	+	125	++	250
17b	++	125	++	250	++	125	++	250	++	250
19	++	250	+++	500	++	250	+	125	++	500
22	++	250	+++	125	++	125	+	125	+	250
24	++	125	+	250	++	250	+	250	+	250
Ampicillin	++	125	+++	250	++	125	−	−	−	−
Clotrimazole	−	−−	−	−	−	−	+++	125	+++	250

A, antimicrobial activity of tested compounds; MIC, minimum inhibitory concentration; −, inactive; +, > 5 mm, slightly active; ++, > 7 mm, moderately active; +++, > 9 mm, highly active.

(CH_2), 52.6 ($\underline{CH_2}CH_3$), 65.3 ($\underline{C}$-CN),108.2 (CN), 150.4 (CO), 118.3, 118.9, 120.3, 120.6, 129.2, 141.3 (phenyl ring), 125.3, 126.3, 127.1, 129.5, 130.1, 131.5 (phenyl ring), 146.5, 155.4 (2CO) (saccharinylsulfonamide moiety); Anal. Calcd. for $C_{20}H_{17}N_5O_8S_2$ (519.51): C, 46.24; H, 3.30; N, 13.48%. Found: C, 46.51; H, 3.50; N, 13.10%.

4-(5-Acetyl-4-amino-6-methyl-2-oxo-2*H*-pyran-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (5). A mixture of compound **3** (1.04 g, 2 mmol) and acetylacetone (2 mmol) in 1,4-dioxane (25 mL) containing a catalytic amount of Et_3N (0.4 mL) was heated under reflux for 8 h. The reaction mixture was concentrated *in vacuo* and the formed solid product was collected by filtration and recrystallized from ethanol to give **5**. Yield, 0.70 g (61%); m.p. 166–168°C; IR: ν = 3405–3240 (multiple bands, NH_2, NH), 1710, 1690, 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.10 (s, 3H, CH_3CO), 4.75 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.25–8.12 (m, 8H, ArH), 8.30 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 16.2 (CH_3), 20.1 ($\underline{CH_3}CO$), 81.3 (C-5), 89.5 (C-3), 136.3 (C-4), 141.4 (C-6), 161.2 ($\overline{CO}$), 165.7 (C-2); Anal. Calcd. for $C_{23}H_{19}N_5O_9S_2$ (573.56): C, 48.16; H, 3.34; N, 12.21%. Found: C, 48.32; H, 3.50; N, 12.01%.

4-(5-Acetyl-4-amino-6-hydroxy-2-oxo-1-phenyl-1,2-dihydropyridin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (6). A mixture of compound **3** (1.04 g, 2 mmol) and acetoacetanilide (2 mmol) in 1,4-dioxane (25 mL) containing a catalytic amount of Et_3N (0.4 mL) was heated under reflux for 8 h. The reaction mixture was concentrated *in vacuo* and the formed solid was collected by filtration and recrystallized from 1,4-dioxane to give **6**. Yield, 0.87 g (67%); m.p. 183–185°C; IR: ν = 3495–3200 (multiple bands, OH, NH_2, NH), 1705, 1680, 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.95 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 5.95 (br s, 2H, NH_2), 7.30–8.3 (m, 13H, ArH), 8.35, 8.50 (2s, 2H, NH, and OH, exchangeable); Anal. Calcd. for $C_{28}H_{22}N_6O_9S_2$ (650.64): C, 51.69; H, 3.41; N, 12.92%. Found: C, 51.41; H, 3.19; N, 12.75%.

General procedure for the preparation of compounds 7a–c. A mixture of compound **3** (1.04 g, 2 mmol) and active methylene compounds *viz* malononitrile, ethyl cyanoacetate, and ethyl acetoacetate (2 mmol) in 1,4-dioxane (25 mL) containing a catalytic amount of Et_3N (0.4 mL) was heated under reflux for 10 h. The reaction mixture was cooled to room temperature, poured into crushed ice (20 g), and neutralized with diluted HCl. The resulting solid product was filtered off and recrystallized from proper solvent to give the compounds **7a–c**.

Ethyl 4-amino-5-cyano-6-imino-1-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-1,6-dihydropyridazine-3-carboxylate (7a). Yield, 0.69 g (59%) (DMF-H_2O); m.p. 173–175°C; IR: ν = 3310–3200 (NH_2, NH), 2215 (CN), 1730, 1680 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ = 1.65 (t, 3H, CH_3), 4.60 (q, 2H, CH_2), 4.80 (s, 2H, CH_2), 5.95 (s, 2H, NH_2), 7.18–8.15 (m, 8H, ArH), 8.20, 8.95 (2s, 2H, 2NH, exchangeable); Anal. Calcd. for $C_{23}H_{19}N_7O_8S_2$ (585.57): C, 47.18; H, 3.27; N, 16.74%. Found: C, 47.37; H, 3.51; N, 16.41%.

Ethyl 4-amino-5-cyano-6-oxo-1-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-1,6-dihydropyridazine-3-carboxylate (7b). Yield, 0.71 g (61%) (*n*-butanol); m.p. 220–222°C; IR: ν = 3340–3210 (NH_2, NH), 2220 (CN), 1725, 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.45 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 4.75 (s, 2H, CH_2), 5.90 (br s, 2H, NH_2), 7.30–8.41 (m, 8H, ArH), 8.75 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 12.3 (CH_3), 50.3 (CH_2), 80.1 (C-5), 112.3 (CN), 140.2 (C-3), 150.2 (CO), 152.5 (C-6), 156.7 (C-4); Anal. Calcd. for $C_{23}H_{18}N_6O_9S_2$ (586.56): C, 47.10; H, 3.09; N, 14.33%. Found: C, 47.39; H, 3.34; N, 14.10%.

Ethyl 5-acetyl-4-amino-6-oxo-1-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-1,6-dihydropyridazine-3-carboxylate (7c). Yield, 0.86 g (71%) (1,4-dioxane); m.p. 212–214°C; IR: ν = 3230 (NH), 2225–2220 (CN), 1680–1675 cm^{-1} (CO); MS: *m*/*z* = 603 (M^+); Anal. Calcd. for $C_{24}H_{21}N_5O_{10}S_2$ (603.58): C, 47.76; H, 3.51; N, 11.60%. Found: C, 47.93; H, 3.75; N, 11.85%.

General procedure for the preparation of compounds 9a,b. A mixture of compound **3** (1.04 g, 2 mmol) and benzylidenemalononitrile or ethyl α-cyanocinnamate (2 mmol) in 1,4-dioxane (20 mL) containing a catalytic amount of triethylamine (0.4 mL) was heated under reflux for 9 h. The reaction mixture

was cooled at room temperature, poured onto ice (20 g), and neutralized with diluted HCl. The formed solid product was filtered off and recrystallized from proper solvent to give **9a,b**.

4-(3,5-Dicyano-4-oxo-6-phenyl-4*H*-pyridazin-1-yl)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (9a). Yield, 0.88 g (73%) (benzene); m.p. 241–243°C; IR: ν = 3310 (NH), 2220–2215 (CN), 1705, 1680–1670, cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 4.60 (s, 2H, CH_2), 7.40–8.31 (m, 13H, ArH), 8.45 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{27}H_{16}N_6O_7S_2$ (600.58): C, 54.00; H, 2.69; N, 13.99%. Found: C, 54.26; H, 2.81; N, 13.79%.

Ethyl 6-cyano-5-oxo-3-phenyl-2-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenyl}-2,5-dihydropyridazine-4-carboxylate (9b). Yield, 0.90 g (69%) (ethanol); m.p. 193–195°C; IR: ν = 3290 (NH), 2215 (CN), 1725, 1705, 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 1.55 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 4.50 (s, 2H, CH_2), 7.20–8.35 (m, 13H, ArH), 8.40 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{29}H_{21}N_5O_9S_2$ (647.64): C, 53.78; H, 3.27; N, 10.81%. Found: C, 53.95; H, 3.51; N, 10.59%.

4-(6-Cyano-5-oxo-4-phenyl-3-thioxo-4,5-dihydro-3*H*-[1,2,4]triazin-2-yl)-*N*-[2-saccharin-2-yl]acetyl]benzenesulfonamide (11). A mixture of compound **3** (1.04 g, 2 mmol) and phenyl isothiocyanate (2 mmol) in 1,4-dioxane (20 mL) containing triethylamine (0.4 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temperature, poured onto cold water (40 mL) and neutralized with dilute HCl. The solid product that formed was collected by filtration and recrystallized from ethanol to give **11**. Yield, 0.93 g (76%); m.p. 211–213°C; IR: ν = 3290 (NH), 2215 (CN), 1685–1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.55 (s, 2H, CH_2), 7.12–8.25 (m, 13H, ArH), 8.35 (s, 1H, NH, exchangeable); Anal. Calcd. for $C_{25}H_{16}N_6O_7S_3$ (608.63): C, 49.34; H, 2.65; N, 13.81%. Found: C, 49.10; H, 2.31; N, 13.96%.

General procedure for the preparation of compounds 12a,b. To a solution of compound **3** (1.04 g, 2 mmol) in ethanolic sodium ethoxide solution (25 mL) [prepared by dissolving sodium metal (2.0 g) in absolute ethanol (20 mL)], urea or thiourea (2 mmol) was added. The reaction mixture was heated under reflux for 8 h. The solvent was evaporated *in vacuo* and the residue was triturated with cold water. The solid formed was collected by filtration and recrystallized from proper solvent to give **12a,b**.

4-(6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (12a). Yield, 0.73 g (68%) (DMF); m.p. 251–253°C; IR: ν = 3400–3230 (NH_2, NH), 1680–1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.61 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.25–8.05 (m, 8H, ArH), 8.10–8.50 (br s, 3H, 3NH, exchangeable); Anal. Calcd. for $C_{19}H_{15}N_7O_8S_2$ (533.50): C, 42.78; H, 2.83; N, 18.38%. Found: C, 42.96; H, 2.98; N, 18.10%.

4-(6-Amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (12b). Yield, 0.80 g (73%); (1,4-dioxane); m.p. 230–232°C; IR: ν = 3395–3200 (NH_2, NH), 1685–1680 cm^{-1} (CO), 1260 cm^{-1} (CS); ^1H NMR ($CDCl_3$): δ = 4.65 (s, 2H, CH_2), 5.90 (br s, 2H, NH_2), 7.30–8.20 (m, 8H, ArH), 8.30–9.00 (br s, 3H, 3NH, exchangeable); Anal. Calcd. for $C_{19}H_{15}N_7O_7S_3$ (549.56): C, 41.52; H, 2.75; N, 17.84%. Found: C, 41.20; H, 2.49; N, 17.98%.

4-(5-Amino-3-hydroxy-1*H*-pyrazol-4-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (13). A mixture of compound **3** (5.19 g, 10 mmol) and hydrazine hydrate (0.6 g, 12 mmol) in absolute ethanol (25 mL) was heated under reflux for 2 h. The solid product which formed after cooling was filtered off and recrystallized from 1,4-dioxane to give **13**. Yield, 3.94 g (78%); m.p. 207–209°C; IR: ν = 3450–3200 (OH, NH_2, NH), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.50 (s, 2H, CH_2), 5.80 (br s, 2H, NH_2), 7.15–8.25 (m, 8H, ArH), 8.30–9.10 (br s, 3H, 2NH, and OH, exchangeable); ^{13}C NMR: δ 62.3 (C-4), 153.3 (C-5), 156.2 (C-3); Anal. Calcd. for $C_{18}H_{15}N_7O_7S_2$ (505.49): C, 42.77; H, 2.99; N, 19.40%. Found: C, 42.50; H, 2.71; N, 19.67%.

4-(5,7-Dimethyl-2-hydroxypyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (14). A mixture of compound **13** (1.01 g, 2 mmol) and acetylacetone (3 mmol) in glacial acetic acid (20 mL) was refluxed for 5 h. The reaction mixture was cooled, the separated solid was filtered off, washed with water and recrystallized from 1,4-dioxane to give **14**. Yield, 0.83 g (73%); m.p. 196–198°C; IR: ν = 3420–3290 (OH, NH), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 1.2–1.4 (br s, 6H, $2CH_3$), 4.55 (s, 2H, CH_2), 7.13–8.10 (m, 9H, ArH), 8.30–8.50 (br s, 2H, NH, and OH, exchangeable); Anal. Calcd. for $C_{23}H_{19}N_7O_7S_2$ (569.57): C, 48.50; H, 3.36; N, 17.21%. Found: C, 48.28; H, 3.12; N, 17.36%.

General procedure for the preparation of compounds 15a,b. A mixture of compound **13** (1.01 g, 2 mmol), benzaldehyde and/or 4-methoxybenzaldehyde (2 mmol) in absolute ethanol (25 mL) was heated under reflux for 5 h. The reaction mixture was cooled and the formed solid was filtered off and recrystallized to give **15a,b**.

4-[5-(Benzylideneamino)-3-hydroxy-1*H*-pyrazol-4-ylazo]-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (15a). Yield, 0.80 g (67%) (ethanol); m.p. 174–176°C; IR: ν = 3490–3290 (OH, NH), 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.60 (s, 2H, CH_2), 7.25–8.30 (m, 14H, ArH, and benzylic proton), 8.40, 8.60, 9.10 (3s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{25}H_{19}N_7O_7S_2$ (593.59): C, 50.58; H, 3.23; N, 16.52%. Found: C, 50.74; H, 3.49; N, 16.23%.

4-{3-Hydroxy-5[(4-methoxybenzylidene)amino]-1*H*-pyrazolo-4-ylazo}-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (15b). Yield–0.79 g (63%) (ethanol); m.p. 213–215°C; IR: ν = 3480–3210 (OH, NH), 1675 cm^{-1} (CO); Anal. Calcd. for $C_{26}H_{21}N_7O_8S_2$ (623.62): C, 50.08; H, 3.39; N, 15.72%. Found: C, 50.30; H, 3.63; N, 15.42%.

General procedure for the preparation of compounds 16a,b. Method A: A mixture of compounds **15a** or **15b** (2 mmol) and malononitrile (0.13 g, 2 mmol) in absolute ethanol (20 mL) containing piperidine (0.4 mL) was heated under reflux for 8 h. The separated solid was filtered off and recrystallized from 1,4-dioxane to give **16a,b**. Yield, 0.73 g (61% for **16a**) and 0.86 g (62% for **16b**).

Method B: A mixture of compound **13** (1.01 g, 2 mmol) and arylidene malononitriles (2 mmol) in 1,4-dioxane (25 mL) containing a few drops of piperidine (0.4 mL) was refluxed for 10 h. The obtained solid after cooling was recrystallized from 1,4-dioxane to give **16a,b**. Yield, 0.82 g (69% for **16a**) and 0.98 g (71% for **16b**).

4-(7-Amino-6-cyano-2-hydroxy-5-phenyl-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (16a). m.p. 165–167°C, IR: ν = 3505–3200 (OH, NH_2, NH), 2215 (CN), 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.50 (s, 2H, CH_2), 5.10 (s, 1H, CH), 5.70 (br s, 2H, NH_2), 7.21–8.11 (m, 13H, ArH), 8.20–9.10 (br s, 3H,

2NH, OH, exchangeable); ^{13}C NMR: δ = 36.3 (C-5), 47.8 (C-6), 60.1 (C-3), 110.3 (CN), 150.1 (C-3a), 151.2 (C-7), 156.3 (C-2), 120.1, 120.4, 123.2, 123.6, 124.2, 129.3 (phenyl ring); Anal. Calcd. for $C_{28}H_{21}N_9O_7S_2$ (659.65): C, 50.98; H, 3.21; N, 19.11%. Found: C, 50.63; H, 3.08; N, 19.37%.

4-[7-Amino-6-cyano-2-hydroxy-5-(4-methoxyphenyl)-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo]-*N*-[2–(saccharin-2-yl)acetyl]benzenesulfonamide (16b). m.p. 190–192°C, IR: ν = 3490–3210 (OH, NH_2, NH), 2220 (CN), 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 3.90 (s, 3H, OCH_3), 4.55 (s, 2H, CH_2), 4.95 (s, 1H, CH), 5.75 (br s, 2H, NH_2), 7.20–8.15 (m, 12H, ArH), 8.30–9.10 (br s, 3H, 2NH, OH, exchangeable); Anal. Calcd. for $C_{29}H_{23}N_9O_8S_2$ (689.68): C, 50.50; H, 3.36; N, 18.28%. Found: C, 50.76; H, 3.60; N, 18.10%.

General procedure for the preparation of compounds 17a,b. Method A: A mixture of compounds **15a** or **15b** (2 mmol) and ethyl cyanoacetate (2 mmol) in absolute ethanol (20 mL) containing piperidine (0.4 mL) was heated under reflux for 8 h. The formed solid was filtered off and recrystallized from *n*-butanol to give **17a,b**. Yield, 0.91 g (64% for **17a**) and 0.89 g (60% for **17b**).

Method B: A mixture of compound **13** (1.01 g, 2 mmol) and β-aryl-α-cyanoacrylate derivatives (2 mmol) in 1,4-dioxane (20 mL) containing piperidine (0.3 mL) was refluxed for 10 h. The resulting solid was filtered off and recrystalized from *n*-butanol to give **17a,b**. Yield, 1.02 g (72% for **17a**) and 1.08 g (73% for **17b**).

Ethyl 7-amino-2-hydroxy-5-phenyl-3-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenylazo}-4,5-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (17a). m.p. 236–238°C, IR: ν = 3490–3180 (OH, NH_2, NH), 1730, 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.60 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 4.65 (s, 2H, CH_2), 5.20 (s, 1H, CH), 5.70 (br s, 2H, NH_2), 7.20–8.15 (m, 13H, ArH), 8.50–9.55 (br s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{30}H_{26}N_8O_9S_2$ (706.71): C, 50.99; H, 3.71; N, 15.86%. Found: C, 50.81; H, 3.50; N, 15.97%.

Ethyl 7-amino-2-hydroxy-5-(4-methoxyphenyl)-3-{4-[2-(saccharin-2-yl)acetylsulfamoyl]phenylazo}-4,5-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (17b). m.p. 203–205°C, IR: ν = 3490–3190 (OH, NH_2, NH), 1725, 1670 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ = 1.70 (t, 3H, CH_3), 3.95 (s, 1H, OCH_3), 4.40 (q, 2H, CH_2), 4.60 (s, 2H, CH_2), 5.15 (s, 1H, CH), 5.75 (br s, 2H, NH_2), 7.15–8.20 (m, 12H, ArH), 8.25–9.50 (br s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{31}H_{28}N_8O_{10}S_2$ (736.73): C, 50.54; H, 3.83; N, 15.21%. Found: C, 50.35; H, 3.60; N, 15.36%.

4-(7-Amino-6-cyano-2-hydroxypyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (19). A mixture of **13** (1.01 g, 2 mmol) and ethoxymethylenemalononitrile (0.22 g, 2 mmol) in DMF (25 mL) containing a few drops of piperidine (0.3 mL) was heated under reflux for 4 h. The reaction mixture was cooled and the formed solid was filtered off and recrystallized from 1,4-dioxane to give **19**. Yield, 0.67 g (58%); m.p. 211–213°C; IR: ν = 3480–3190 (OH, NH_2, NH), 2215 (CN), 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 4.60 (s, 2H, CH_2), 5.95 (br s, 2H, NH_2), 7.15–8.20 (m, 9H, ArH), 8.60–9.10 (br s, 2H, NH, and OH, exchangeable); ^{13}C NMR: δ = 35.6 (C-6), 82.1 (C-3), 111.2 (CN), 140.2 (C-3a), 150.3 (C-5), 153.1 (C-7), 156.3 (C-2); Anal. Calcd. for $C_{22}H_{15}N_9O_7S_2$ (581.54): C, 45.44; H, 2.60; N, 21.68%. Found: C, 45.65; H, 2.81; N, 21.45%.

4-(6-Cyano-2-hydroxy-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (20). A mixture of **13** (1.01 g, 2 mmol) and ethyl ethoxymethylenecyanoacetate (0.34 g, 2 mmol) in DMF (20 mL) containing a few drops of piperidine (0.4 mL) was refluxed for 4 h. The reaction mixture was cooled and the formed solid was filtered off and recrystallized from DMF to give **20**. Yield, 0.65 g (56%); m.p. 196–198°C; IR: ν = 3490–3180 (OH, NH), 2210 (CN), 1680–1675 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ = 4.55 (s, 2H, CH_2), 7.15–8.10 (m, 9H, ArH), 8.60–9.10 (br s, 3H, 2NH, and OH, exchangeable); Anal. Calcd. for $C_{22}H_{14}N_8O_8S_2$ (582.53): C, 45.36; H, 2.42; N, 19.24%. Found: C, 45.53; H, 2.61; N, 19.41%.

4-(5,7-Diamino-2-hydroxy-6-phenylazopyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (22). A mixture of **13** (1.01 g, 2 mmol) and 2-phenylhydrazonomalononitrile (0.34 g, 2 mmol) in absolute ethanol (20 mL) containing a few drops of pyridine (0.4 mL) was heated under reflux for 6 h, then allowed to cool at room temperature. The precipitated solid was filtered off, washed with water (3 × 30 mL) and recrystallized from *n*-butanol to give **22**. Yield, 0.85 g (63%); m.p. 186–188°C; IR: ν = 3495–3180 (OH, NH_2, NH), 1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 4.61 (s, 2H, CH_2), 5.85–6.10 (br s, 4H, $2NH_2$), 7.10–8.15 (m, 13H, ArH), 8.50–8.75 (br s, 2H, NH, and OH, exchangeable); Anal. Calcd. for $C_{27}H_{21}N_{11}O_7S_2$ (675.66): C, 48.00; H, 3.13; N, 22.80%. Found: C, 48.26; H, 3.36; N, 22.51%.

4-(7-Amino-2-hydroxy-5-oxo-6-phenylazo-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-ylazo)-*N*-[2-(saccharin-2-yl)acetyl]benzenesulfonamide (24). A mixture of **13** (1.01 g, 2 mmol) and ethyl 2-phenylhydrazonocyanoacetate (0.43 g, 2 mmol) in absolute ethanol (20 mL) containing a few drops of pyridine (0.5 mL) was heated under reflux for 6 h, then allowed to cool at room temperature. The formed solid was filtered off, washed with water (3 × 30 mL) and recrystallization from DMF to give **24**. Yield, 0.82 g (61%); m.p. 201–203°C; IR: ν = 3490–3200 (OH, NH_2), 1680–1675 cm^{-1} (CO); ^{1}H NMR (DMSO = d_6): δ = 4.50 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.26–8.20 (m, 13H, ArH), 8.40–9.10 (br s, 3H, 2NH, and OH, exchangeable); ^{13}C NMR: δ = 67.1 (C-6), 68.5 (C-3), 131.5 (C-3a), 148.5 (C-7), 152.1 (C-2), 154.2 (C-5), 120.1, 120.9, 121.2, 121.8, 122.5, 123.1 (phenyl ring); Anal. Calcd. for $C_{27}H_{20}N_{10}O_8S_2$ (676.64): C, 47.93; H, 2.98; N, 20.70%. Found: C, 47.75; H, 2.71; N, 20.50%.

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