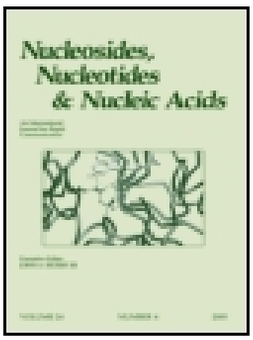

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Purine and Guanine Thioglycoside Analogs: Novel Synthesis of a New Class of Pyrazolo[1,5-A][1,3,5]Triazine-4-Thioglycoside Derivatives under Microwave Activation

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PURINE AND GUANINE THIOGLYCOSIDE ANALOGS: NOVEL SYNTHESIS OF A NEW CLASS OF PYRAZOLO[1,5-A][1,3,5]TRIAZINE-4-THIOGLYCOSIDE DERIVATIVES UNDER MICROWAVE ACTIVATION

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□ *A first microwave-assisted synthesis of a new class of novel purine thioglycoside analogues from readily available starting materials has been described. The key step of this protocol is the formation of sodium pyrazolo[1,5-a][1,3,5]triazine-4-thiolates via condensation of 5-amino-1H-pyrazoles with sodium cyanocarbonimidodithioate salt under microwave irradiation, followed by coupling with halo sugars to give the corresponding purine thioglycoside analogues. Further studies on the application of this method for the synthesis of other highly functionalized biologically active glycosides are underway.*

Keywords Microwave synthesis; purine thioglycoside analogues; thioglycosides; sodium cyanocarbonimidodithioate salt; anti-metabolites

INTRODUCTION

6-Mercaptopurine (6-MP) is commonly referred by pharmacists as *purinethol*. It is listed as an anti-neoplastic and immunosuppressant. 6-MP is a DNA anti-metabolite. This means that it mimics the substance necessary in DNA synthesis.[1] In the body, 6-MP is converted into the corresponding ribonucleotide. 6-MP ribonucleotide is a potent inhibitor of the conversion of the compound called inosinic acid to adenylic acid. Without adenylic acid, DNA cannot be synthesized. 6-MP also works by being incorporated into nucleic acids as thioguanosine, rendering the resulting nucleic acids (DNA, RNA) unable to direct proper protein synthesis.[2] 6-Thioguanine (6-TG) is closely related to 6-MP in both structure and metabolism. Similar to 6-MP, 6-TG is a purine anti-metabolite. Thioguanine inhibits purine biosynthesis as does 6-MP, albeit at different steps.[3] 6-MP and 6-TG are the only two purine

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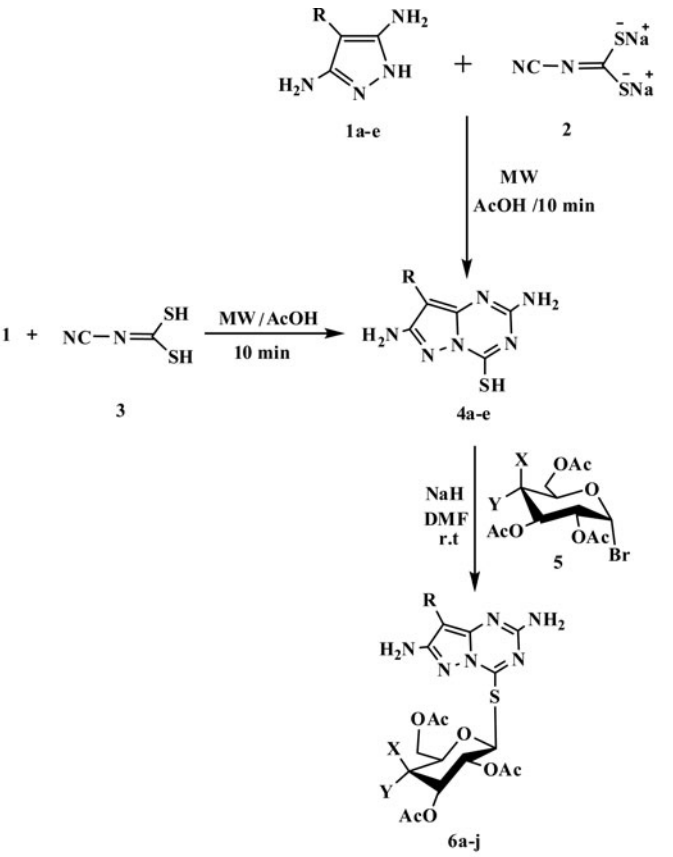
anti-metabolites that are currently used in chemotherapy.[4] 6-MP and 6-TG have certain therapeutic disadvantages, which have continued to stimulate the search for purine analogs enhancing therapeutic efficacy.[5] Considerable efforts have been made to prepare other novel mercaptopurine and thioguanine analogs and their nucleosides to improve anti-tumor efficacy; very few examples are reported for the synthesis of purine and guanine thioglycosides. In recent reports from our laboratory, we described the preparation of different novel functionalized heterocyclic thioglycosides.[6–12] In an earlier brief communication, we had already reported the use of dihydropyridine thioglycosides as substrates or inhibitors in the protein glycosylation process.[13,14] These common features encouraged us to develop a new straightforward route for the synthesis of guanine and purine thioglycosides. Continuing our efforts for the development of simple, eco-friendly and cost-effective methodologies,[15] we report here in this research a novel microwave-assisted synthesis of thioguanine and mercaptopurine analogues and their thioglycosides as anti-metabolic agents. As far as we know, this is the first method to be reported for the preparation of such a novel ring system.

RESULTS AND DISCUSSION

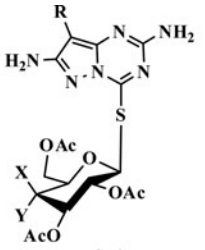
It has been found that reaction of cyanamide with carbon disulfide in the presence of sodium ethoxide gives sodium cyanocarbonimidodithioate salt **2**. Compounds **2** are readily reacted with one equivalent of 5-aminopyrazoles **1a-e** in the presence of acetic acid under microwave activation for 10 min to give the corresponding pyrazolo[1,5-*a*][1,3,5]triazine-4-thiol derivatives **4a-e** in good yields. The structures of **4a-e** were established on the basis of its elemental analysis and spectral data (IR, ^{1}H NMR, and ^{13}C NMR). Compounds **4a-e** can also be prepared through the reaction of cyanocarbonimidodithioic acid **3** with 5-aminopyrazoles **1a-e** under the same reaction conditions. Compounds **4a-e** reacted with halosugars **5** in dimethylformamide at room temperature to give in high yield the corresponding *S*-glycosides **6a-j** (Scheme 1). It has been suggested that the *cis*-(α) sugars react by a simple SN_2 reaction to give the β-glycoside products.[16] The structures of **6a-j** were established on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR, and ^{13}C NMR). For example, the analytical data for **6a** revealed a molecular formula $C_{25}H_{28}N_8O_9S$, its ^{1}H NMR spectrum showing the anomeric proton as a doublet at δ 5.29–5.32 ppm with a spin–spin coupling constant of 11.25 Hz indicating the β-configuration. The other six glucose protons resonated at δ 3.73–4.82 ppm. When glycosides **6a-j** were treated with methanolic ammonia at room temperature for 10 min, the deprotected derivatives **7a-j** were obtained in almost quantitative yields (Scheme 2), the structures of which were established



6	R	X	Y	6	R	X	Y
a	C_6H_5-N=N-	H	OAc	f	C_6H_5-N=N-	OAc	H
b	4-MeO-C_6H_4-N=N-	H	OAc	g	4-MeO-C_6H_4-N=N-	OAc	H
c	4-Me-C_6H_4-N=N-	H	OAc	h	4-Me-C_6H_4-N=N-	OAc	H
d	4-Cl-C_6H_4-N=N-	H	OAc	i	4-Cl-C_6H_4-N=N-	OAc	H
e	4-Br-C_6H_4-N=N-	H	OAc	j	4-Br-C_6H_4-N=N-	OAc	H

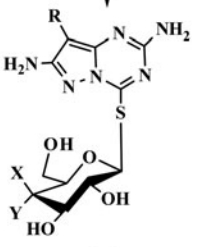
SCHEME 1 Synthetic pathway for 4-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glycopyranosylthio)-pyrazolo[1,5-a][1,3,5]triazines 6a-j

on the basis of elemental analysis and spectral data. Thus, the analytical data for **7a** reveal the molecular formula $C_{17}H_{20}N_8O_5S$. The ^{1}H NMR spectrum shows the anomeric proton as a doublet at δ 4.52–4.54 ($J_{1,2}$ = 9.95 Hz), indicating the presence of only β-*D* configuration. The other six-glucose protons appear as a multiplet at δ 3.34–4.41, while the four hydroxy groups of glucose moiety resonated at δ 5.14–5.23 (exchangeable by D_2O). Encouraged by these results, methylation of compounds **4a-e** with methyl iodide in sodium ethoxide gave the 4-methylthiopyrazolo[1,5-*a*][1,3,5]triazine



6a-j

MeOH/ NH_3
r.t /10 min



7a-j

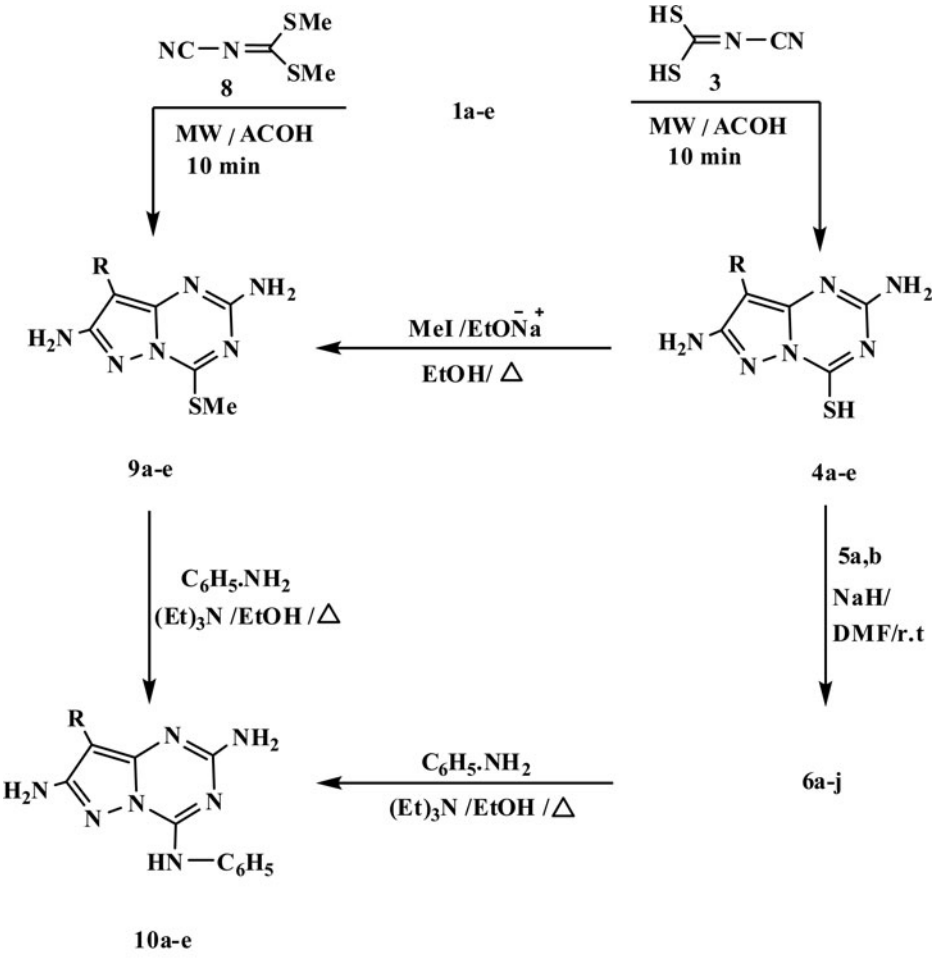
7	R	X	Y	7	R	X	Y
a	C_6H_5-N=N-	H	OH	f	C_6H_5-N=N-	OH	H
b	4-MeO-C_6H_4-N=N-	H	OH	g	4-MeO-C_6H_4-N=N-	OH	H
c	4-Me-C_6H_4-N=N-	H	OH	h	4-Me-C_6H_4-N=N-	OH	H
d	4-Cl-C_6H_4-N=N-	H	OH	i	4-Cl-C_6H_4-N=N-	OH	H
e	4-Br-C_6H_4-N=N-	H	OH	j	4-Br-C_6H_4-N=N-	OH	H

SCHEME 2 Synthetic pathway for 4-(β-D-Glycopyranosylthio)-pyrazolo[1,5-a][1,3,5]triazines 7a-j

products **9a-e**.[10] Compounds **9a-e** can also be prepared by the reaction of **1a-e** with dimethyl *N*-cyanodithioiminocarbonate **8** in acetic acid under microwave activation for 10 min. When compounds **6a-j** and **9a-e** were subjected to reaction with aniline, the corresponding 4-anilinopyrazolo[1,5-*a*][1,3,5]triazine derivatives **10a-e** were obtained [17] (Scheme 3). The structure of compound **10** was established on the basis of elemental analysis and spectral data (MS, ^{1}H NMR, and IR).

CONCLUSIONS

We have developed a new and simple method for the synthesis of purine and guanine thioglycoside analogues under microwave activation. The mild reaction conditions, clean reaction profiles, zero side product, and cost-efficiency render this approach as a useful and innovative one to the existing



4,9,10	R
a	C_6H_5-N=N-
b	4-MeO-C_6H_4-N=N-
c	4-Me-C_6H_4-N=N-
d	4-Cl-C_6H_4-N=N-
e	4-Br-C_6H_4-N=N-

SCHEME 3 Synthetic pathway for pyrazolo[1,5-a][1,3,5]triazines 4a-e, 9a-e, 10a-e

methods for glycoside formation. Further studies on the application of this method for the synthesis of other highly functionalized biologically active glycosides are underway.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The ^{1}H NMR spectra were measured on a Jeol-500 MHz spectrometer for solutions DMSO-d_6 and $CDCl_3$ using $Si(CH_3)_4$ as an internal standard at National Research Centre, Cairo, Egypt. Progress of the reactions was monitored by TLC using aluminum sheets coated with silica gel F254 (Merck). Viewing under a short-wavelength UV lamp effected detection. Microwave reactions were conducted using microwave.

General Procedure for Synthesizing 4a-e

A mixture of 4-(Aryldiazenyl)-1*H*-pyrazole-3,5-diamine **1a-e** (10 mmol) and sodium cyanocarbonimidodithioate **2** or cyanocarbonimidodithioic acid **3** (10 mmol) in a glacial acetic acid (20 mL), irradiated in a microwave oven for 10 min at 150°C, the reaction mixture was cooled to room temperature and triturated with MeOH to afford **4a-e**, which was collected by filtration, and recrystallized from the appropriate solvent.

2,7-Diamino-8-(phenyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-4-thiol (4a)

Yellow solid (MeOH) yield 82%: m.p. 210°C; IR (KBr, cm^{-1}) υ 3447, 3438, 3325 (NH_2), 1610 (C=N), 1599 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.34 (s, 2H, NH_2), 6.65 (s, 2H, NH_2), 7.23–7.47 (m, 5H, C_6H_5), 12.27 (s, 1H, SH); ^{13}C NMR: δ 94.2 (C-8), 129.5 (4C, Ar-C), 129.8 (2C, Ar-C), 136.1 (C-8a), 155.7 (C-7), 180.1 (C-2), 201.2 (C-4); MS. *m/z* (%) [M^+ 286]. Anal. Calcd. for $C_{11}H_{10}N_8S$ (286.32): C, 46.14; H, 3.52; N, 39.14; S, 11.20. Found: C, 46.16; H, 3.45; N, 39.18; S, 11.15.

2,7-Diamino-8-(4-methoxyphenyldiazenyl)pyrazolo[1,5-a][1,3,5] triazine-4-thiol (4b)

Yellow solid (MeOH) yield 82%: m.p. 224°C; IR (KBr, cm^{-1}) υ 3443, 3438, (NH_2), 1609 (C=N), 1599 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.01 (s, 3H, OCH_3), 6.62 (s, 2H, NH_2), 6.68 (s, 2H, NH_2), 7.23–7.49 (m, 4H, C_6H_4), 12.13 (s, 1H, SH); ^{13}C NMR: δ 57.2 (CH_3), 96.4 (C-8), 115.9 (2C, Ar-C), 129.8 (2C, Ar-C), 122.5 (Ar-C), 162.1 (Ar-C), 137.5 (C-8a), 157.8 (C-7), 182.6 (C-2), 200.7 (C-4). Anal. Calcd. for $C_{12}H_{12}N_8OS$ (316.34): C, 45.50; H, 3.80; N, 35.42; S, 10.14. Found: C, 45.56; H, 3.82; N, 35.40; S, 10.10.

2,7-Diamino-8-(p-tolyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-4-thiol (4c)

Yellow solid (MeOH) yield 85%: m.p. 202°C; IR (KBr, cm^{-1}) υ 3456, 3443 (NH_2), 1606 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 6.42 (s, 2H, NH_2), 6.77 (s, 2H, NH_2), 7.34–7.56 (m, 4H, C_6H_4), 12.32 (s, 1H, SH); ^{13}C NMR: δ 22.5 (CH_3), 94.3 (C-8), 127.8 (Ar-C), 129.2 (2C, Ar-C), 130.2 (2C, Ar-C), 138.4 (Ar-C), 133.6 (C-8a), 155.2 (C-7), 180.2 (C-2),

199.8 (C-4). Anal.Calcd. for $C_{12}H_{12}N_8S$ (300.34): C, 47.99; H, 4.03; N, 37.31; S, 10.68. Found: C, 47.90; H, 4.12; N, 37.25; S, 10.56.

2,7-Diamino-8-(4-chlorophenyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-4-thiol (4d)

Yellow solid (MeOH) yield 85%: m.p. 220°C; IR (KBr, cm^{-1}) υ 3457, 3422 (NH_2). ^1H NMR (500 MHz, DMSO-d_6): δ 6.52 (s, 2H, NH_2), 6.68 (s, 2H, NH_2), 7.50–7.81 (m, 4H, C_6H_4), 13.12 (s, 1H, SH); ^{13}C NMR: δ 93.8 (C-8), 128.2 (Ar-C), 129.6 (2C, Ar-C), 131.4 (2C, Ar-C), 135.3 (Ar-C), 134.2 (C-8a), 156.4 (C-7), 180.6 (C-2), 200.1 (C-4). Anal.Calcd. for $C_{11}H_9ClN_8S$ (320.76): C, 41.19; H, 2.83; N, 34.93; S, 10.00. Found: C, 41.21; H, 2.90; N, 34.90; S, 10.11.

2,7-Diamino-8-(4-bromophenyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-4-thiol (4e)

Yellow solid (MeOH), yield 80%: m.p. 215°C; IR (KBr, cm^{-1}) υ 3472, 3423, 3328 (NH_2). ^1H NMR (500 MHz, DMSO-d_6): δ 6.58 (s, 2H, NH_2), 6.66 (s, 2H, NH_2), 7.43–7.68 (m, 4H, C_6H_4), 12.54 (s, 1H, SH). Anal.Calcd. for $C_{11}H_9BrN_8S$ (365.21): C, 36.18; H, 2.48; N, 30.68; S, 8.78. Found: C, 36.20; H, 2.40; N, 30.65; S, 8.76.

General Procedures for synthesizing (6a-j)

To a solution of **4a-e** (10 mmol) in dry DMF (20 mL), NaH (15 mmol) was added portion-wise through 15 min, and the solution was stirred at room temperature for another 1 h, a cooled solution of 2,3,4,6-tetra-O-acetyl-α-D-gluco (or galacto)pyronosyl bromide (10 mmol) **5** was dropped within 30 min and the reaction mixture was stirred at room temperature until completion (TLC, 6–8 h). After completion, the reaction mixture was poured on ice water. A solid product precipitate was filtered off. Dried, purified on silica gel column using petroleum ether 40–60°C: ethyl acetate (4:1) as an eluent and recrystallized from appropriate solvent to give compounds **6a-j**.

4-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosylthio)-8- (phenyldiazenyl)pyrazolo[1,5a][1,3,5]triazine-2,7-diamine (6a)

Yellow solid (MeOH); yield 79%; m.p. 185°C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.96–2.12 (4s, 12H, 4xOAc), 3.73, 4.04 (m, 2H, 2H-6'), 4.25 (m, H, H-4'), 4.50 (m, 1H, H-5'), 4.59 (t, $J = 9.2$ Hz, 1H, H-3'), 4.82 (t, $J = 9.1$ Hz, 1H, H-2'), 5.29–5.32 (d, $J_{1'-2'} = 11.25$ Hz, 1H, H-1'), 6.37 (s, D_2O exch., 2H, NH_2), 6.31 (s, D_2O exch., 2H, NH_2). ^{13}C NMR: δ 62.4 (C-6'), 67.4 (C-4'), 69.4 (C-2'), 70.8 (C-3'), 75.6 (C-5'), 81.2 (C-1'), 94.2 (C-8), 128.7 (4C, Ar-C), 129.1 (2C, Ar-C), 135.3 (C-8a), 155.4 (C-7), 170.4 (4CO), 181.2 (C-2), 183.2 (C-4). Anal. Calcd. for $C_{25}H_{28}N_8O_9S$ (616.60): C, 48.70; H, 4.58; N, 18.17; S, 5.20. Found: C, 48.65; H, 4.50; N, 18.10; S, 5.25.

8-(4-Methoxyphenyldiazenyl)-4-(2',3',4',6'-tetra-O-acetyl-β-D- glucopyranosyl thio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6b)

Yellow solid (MeOH); yield 75%; m.p. 190°C; IR (KBr, cm^{-1}) υ 3454, 3433, 3332 (NH_2), 1736 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.97–2.21 (4s, 12H, 4xOAc), 3.78 (s, 3H, OCH_3), 3.92–4.02 (m, 2H, 2H-6'), 4.16 (m, 1H, H-5'), 4.23 (t, J = 9.1 Hz, 1H, H-4'), 4.42 (t, J = 9.3 Hz, 1H, H-3'), 5.18 (t, J = 9.2, 1H, H-2'), 5.23–5.24 (d, $J_{1'-2'}$ = 5.01, 1H, Hz, H-1'), 6.32 (s, 2H, NH_2), 6.53 (s, 2H, NH_2), 7.23–7.52 (m, 4H, C_6H_4).^{13}C NMR: δ 22.0 ($4CH_3CO$), 57.6 (CH_3), 62.6 (C-6'), 69.6 (C-4'), 70.4 (C-2'), 74.2 (C-3'), 77.1 (C-5'), 84.2 (C-1'), 93.8 (C-8), 116.5 (2C, Ar-C), 124.1 (Ar-C), 131.5 (2C, Ar-C), 135.3 (C-8a), 156.6 (C-7), 162.4 (Ar-C), 170.4 (4CO), 182.4 (C-2), 184.5 (C-4). Anal.Calcd. for $C_{26}H_{30}N_8O_{10}S$ (646.63): C, 48.29; H, 4.68; N, 17.33; S, 4.96. Found: C, 48.25; H, 4.62; N, 17.35; S, 4.90.

4-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosylthio)-8-(p-tolyldiazenyl)pyra zolo[1,5-a][1,3,5]triazine-2,7-diamine (6c)

Yellow solid (MeOH); yield 80%; m.p. 177°C; IR (KBr, cm^{-1}) υ 3431, 3380, 3332 (NH_2), 1743 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.97–2.21 (4s, 12H, 4xOAc), 2.99 (s, 3H, CH_3), 3.95 (m, 2H, 2H-6'), 4.14 (m, 1H, H-5'), 4.41 (t, J = 9.3 Hz, 1H, H-4'), 4.56 (t, J = 9.1 Hz, 1H, H-3'), 4.79 (t, J = 9.2, 1H, H-2'), 5.09–5.12 (d, $J_{1'-2'}$ = 5.70, 1H, Hz, H-1'), 6.43 (s, 2H, NH_2), 6.51 (s, 2H, NH_2), 7.26–7.34 (m, 4H, C_6H_4).^{13}C NMR: δ 21.9 ($4CH_3$.CO), 24.2 (CH_3), 62.2 (C-6'), 68.8 (C-4'), 70.6 (C-2'), 75.5 (C-3'), 76.6 (C-5'), 82.1 (C-1'), 90.9 (C-8), 130.4 (2C, Ar-C), 125.0 (Ar-C 1321.8 (2C, Ar-C), 140.2 (Ar-C), 136.5 (C-8a), 155.5 (C-7), 170.8 (4CO), 180.3 (C-2), 182.4 (C-4). Anal.Calcd. for $C_{26}H_{30}N_8O_9S$ (630.63): C, 49.52; H, 4.79; N, 17.77; S, 5.08. Found: C, 49.50; H, 4.75; N, 17.80; S, 5.15.

8-(4-Chlorophenyldiazenyl)-4-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl thio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6d)

Pale yellow solid (MeOH); yield 72%; m.p. 179°C; IR (KBr, cm^{-1}) υ 3434, 3396, 3342 (NH_2), 1736 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.95–2.16 (4s, 12H, 4xOAc), 3.92 (m, 2H, 2H-6'), 4.15 (m, 1H, H-5'), 4.73 (t, J = 9.5 Hz, 1H, H-4'), 4.95 (t, J = 9.4 Hz, 1H, H-3'), 5.35 (t, J = 9.2, 1H, H-2'), 5.55–5.57 (d, $J_{1'-2'}$ = 9.20, 1H, Hz, H-1'), 6.58 (s, 2H, NH_2), 6.81 (s, 2H, NH_2), 7.36–7.68 (m, 4H, C_6H_4). Anal. Calcd. for $C_{25}H_{27}ClN_8O_9S$ (651.05): C, 46.12; H, 4.18; N, 17.21; S, 4.93. Found: C, 46.15; H, 4.20; N, 17.25; S, 4.90.

8-(4-Bromophenyldiazenyl)-4-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl thio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6e)

Pale yellow solid (MeOH); yield 71%; m.p. 185°C; IR (KBr, cm^{-1}) υ 3447, 3384, 3339 (NH_2), 1739 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09–2.16 (4s, 12H, 4xOAc), 3.90 (m, 2H, 2H-6'), 4.15–4 24 (m, 2H, H-5', H-4'), 4.64

(t, J = 9.5 Hz, 1H, H-3'), 4.92 (t, J = 9.2, 1H, H-2'), 5.47–5.49 (d, $J_{1'-2'}$ = 9.11, 1H, Hz, H-1'), 6.65 (s, 2H, NH_2), 6.88 (s, 2H, NH_2), 7.33–7.63 (m, 4H, C_6H_4). Anal. Calcd. for $C_{25}H_{27}BrN_8O_9S$ (695.50): C, 43.17; H, 3.91; N, 16.11; S, 4.61. Found: C, 43.15; H, 3.90; N, 16.8; S, 4.55.

4-(2',3',4',6'-Tetra-O-acetyl-β-D-galactopyranosylthio)-8-(phenyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6f)

Yellow solid (MeOH); yield 80%; m.p. 191°C; IR (KBr, cm^{-1}) υ 3434, 3395, 3341 (NH_2), 1745 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.84–2.08 (4s, 12H, 4xOAc), 4.02 (m, 2H, 2H-6'), 4.37 (m, H, H-5'), 5.11 (t, J = 9.3 Hz, 1H, H-4'), 5.22 (t, J = 9.2, 1H, H-3'), 5.24 (t, J = 9.1 Hz, H-2'), 6.21 (d, $J_{1'-2'}$ = 10.35, 1H, Hz, H-1'), 6.57 (s, 2H, NH_2), 6.85 (s, 2H, NH_2), 7.34–7.88 (m, 5H, C_6H_5). Anal. Calcd. for $C_{25}H_{28}N_8O_9S$ (616.60): C, 48.70; H, 4.58; N, 18.17; S, 5.20. Found: C, 48.65; H, 4.50; N, 18.20; S, 5.25.

8-(4-Methoxyphenyldiazenyl)-4-(2',3',4',6'-tetra-O-acetyl-β-D- galactopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6g)

Yellow solid (MeOH); yield 79%; m.p. 174°C; IR (KBr, cm^{-1}) υ 3437, 3396, 3339 (NH_2), 1741 (CO). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93–2.12 (4s, 12H, 4xOAc), 3.82 (s, 3H, OCH_3), 3.92–4.28 (m, 3H, 2H-6', H-5'), 4.02 (m, 1H, H-4'), 4.63 (t, J = 9.22, H, H-3'), 5.14 (t, J = 9.5, 1H, H-2'), 5.42 (d, $J_{1'-2'}$ = 8.56 Hz, 1H, H-1'), 6.64 (s, 2H, NH_2), 6.81 (s, 2H, NH_2), 7.34–7.89 (m, 4H, C_6H_4). ^{13}C NMR: δ 20.6 ($4CH_3$.CO), 58.1 (s, 3H, CH_3O), 62.3 (C-6'), 63.3 (C-5'), 67.6 (C-4'), 72.2 (C-3'), 74.0 (C-2'), 79.6 (C-1'), 93.6 (C-8), 116.4 (2C, Ar-C), 132.2 (2C, Ar-C), 123.4 (Ar-C), 164.2 (Ar-C), 136.2 (8a), 158.4 (C-7), 170.2 (4CO), 177.2 (C-2), 185.1 (C-4). Anal. Calcd. for $C_{26}H_{30}N_8O_{10}S$ (646.63): C, 48.29; H, 4.68; N, 17.33; S, 4.96. Found: C, 48.30; H, 4.70; N, 17.30; S, 4.90.

4-(2',3',4',6'-Tetra-O-acetyl-β-D-galactopyranosylthio)-8-(p-tolyldiazenyl) pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6h)

Yellow solid (MeOH); yield 70%; m.p. 172°C.; IR (KBr, cm^{-1}) υ 3427, 3301 (NH_2), 1745 (CO). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.12 (4s, 12H, 4xOAc), 3.02 (s, 3H, CH_3), 3.95–4.21 (m, 3H, 2H-6', H-5'), 4.15 (m, 1H, H-4'), 4.35 (t, J = 9.5, H, H-3'), 3.82 (t, J = 9.2, 1H, H-2'), 5.53 (d, $J_{1'-2'}$ = 9.64 Hz, 1H, H-1'), 6.72 (s, 2H, NH_2), 6.84 (s, 2H, NH_2), 7.34–7.56 (m, 4H, C_6H_4). Anal. Calcd. for $C_{26}H_{30}N_8O_9S$ (630.63): C, 49.52; H, 4.79; N, 17.77; S, 5.08. Found: C, 49.50; H, 4.70; N, 17.50; S, 5.20.

8-(4-Chlorophenyldiazenyl)-4-(2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl thio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (6i)

Yellow solid (DMF); yield 75%; m.p. 187°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.03 (4s, 12H, 4CH_3CO), 3.82–4.01 (m, 3H, H-6', H-5'), 4.24 (m, 1H, H-4'), 4.75 (t, J = 9.3, 1H, H-3'), 5.03 (t, J = 9.2, 1H, H-2'), 5.58 (d, 1H, $J_{1'-2'}$ = 8.9 Hz, H-1'), 6.79 (s, 2H, NH_2), 6,84 (s, 2H, NH_2), 7.34–7.51 (m, 4H, C_6H_4).^{13}C NMR: δ 22.2 (4CH_3.CO), 62.6 (C-6'), 67.4 (C-4'), 68.2 (C-2'), 71.1 (C-3'), 72.3 (C-5'), 81.0 (C-1'), 95.21 (C-8), 128.6 (Ar-C), 130.4 (2C, Ar-C), 131.2 (2C, Ar-C), 134.8 (C-8a), 136.2 (Ar-C), 157.4 (C-7), 178.4 (C-2), 171.0 (4CO), 179.1 (C-4). Anal. Calcd. for $C_{25}H_{27}ClN_8O_9S$ (651.05): C, 46.12; H, 4.18N, 17.21S, 4.93. Found: C, 46.22; H, 4.10; N, 17.10; S, 4.80.

8-(4-bromophenyldiazenyl)-4-(2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl thio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine(6j)

Yellow solid (MeOH); yield 72%; m.p. 186°C; IR (KBr, cm^{-1}) υ 3444, 3315 (NH_2), 1743 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.08–2.13 (4s, 12H, 4xOAc), 3.92 (m, 2H, 2H-6'), 4.21–4.23 (m, 2H, H-5', H-4'), 4.44 (t, J = 9.5 Hz, 1H, H-3'), 4.62 (t, J = 9.2, 1H, H-2'), 5.52–5.50 (d, $J_{1'-2'}$ = 9.10, 1H, Hz, H-1'), 6.78 (s, D_2O exch., 2H, NH_2), 6.84 (s, 2H, NH_2), 7.34–7.72 (m, 4H, C_6H_4). Anal. Calcd. for $C_{25}H_{27}BrN_8O_9S$ (695.50): C, 43.17; H, 3.91; N, 16.11; S, 4.61. Found: C, 43.10; H, 3.77; N, 16.6; S, 4.50.

Ammonolysis of (6a-j)

Dry gaseous ammonia was passed through a solution of protected glycosides **6a-j** (10 mmol) in dry methanol (20 mL) at room temperature for 10 min. The mixture was further stirred at room temperature until the reaction was judged complete by TLC (10–12 h) using ($CHCl_3$/MeOH 9:1) (Rf, 0.67–0.69). The resulting mixture was then evaporated under reduced pressure to afford a solid residue that was crystallized from appropriate solvent to give compounds **7a-j**.

4-(β-D-Glucopyranosylthio)-8-(phenyldiazenyl)pyrazolo[1,5-a][1,3,5]triaz ine-2,7-diamine (7a)

Yellowish white solid (MeOH); yield 75%; m.p. 211°C; IR (KBr, cm^{-1}) υ 3620 (OH), 3415, 3342, (NH_2), 1618 (C—N), 1569 (C—C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.34 (m, 2H, 2H-6'), 3.41 (m, 1H, H-5'), 3.53 (t, $J_{4'-3'}$ = 9.2 Hz, 1H, H-4'), 3.74 (t, $J_{3'-2'}$ = 9.2 Hz, $J_{3'-4'}$ = 9.1 Hz, 1H, H-3'), 4.41 (t, $J_{2'-1'}$ = 9.1 Hz, $J_{2'-3'}$ = 9.5, 1H, H-2'), 4.52–4.54 (d, 1H, $J_{1'-2'}$ = 9.95 Hz, H-1'), 5.14 (s, 1H, 2'-OH), 5.23 (m, 3H, 3'-OH, 4'-OH, and 6'-OH), 6.81 (s, 2H, NH_2), 6.88 (s, 2H, NH_2), 7.33–7.52 (m, 5H, C_6H_5). ^{13}C NMR: δ 62.4 (C-6'), 72.5 (C-4'), 75.1 (C-5'), 80.2 (C-3'), 82.1 (C-2'), 91.2 (C-1'), 94.4 (C-8), 130.2 (4C, Ar-C), 131.2 (2C, Ar-C), 135.6 (C-8a), 157.6 (C-7), 183.8

(C-2), 184.8 (C-4). Anal. Calcd. for $C_{17}H_{20}N_8O_5S$ (448.46): C, 45.53; H, 4.50; N, 24.99; S, 7.15. Found: C, 45.45; H, 4.35; N, 24.85; S, 7.20.

8-(4-Methoxyphenyldiazenyl)-4-(β-D-glucopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7b)

Yellowish white solid (MeOH); yield 75%; m.p. 203°C; IR (KBr, cm^{-1}) υ 3610 (OH), 3420, 3349, (NH_2); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.21 (s, 3H, OCH_3), 3.72–4.21 (m, 3H, 2H-6', H-5'), 4.32 (m, 2H, H-4', H-3'), 4.44 (t, $J = 9.2$ Hz, 1H, H-2'), 4.52 (s, 1H, 2'-OH), 4.84 (m, 3H, 3'OH, 4'-OH, and 6'-OH), 5.62 (d, 1H, $J_{1'-2'} = 9.98$ Hz, H-1'), 6.85 (s, 2H, NH_2), 6.88 (s, 2H, NH_2), 7.21–7.42 (m, 4H, C_6H_4). ^{13}C NMR: δ 58.2 (CH_3O), 61.2 (C-6'), 69.6 (C-4'), 71.5 (C-5'), 75.6 (C-3'), 77.5 (C-2'), 82.2 (C-1'), 96.4 (C-8), 117.3 (2C, Ar-C), 125.4 (Ar-C), 132.5 (2C, Ar-C), 136.5 (C-8a), 156.5 (C-7), 165.2 (Ar-C), 181.9 (C-2), 183.6 (C-4). Anal. Calcd. for $C_{18}H_{22}N_8O_6S$ (478.48): C, 45.18; H, 4.63; N, 23.42; S, 6.70. Found: C, 45.30; H, 4.50; N, 23.30; S, 6.60.

4-(β-D-Glucopyranosylthio)-8-(p-tolyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7c)

Yellowish white solid (MeOH); yield 75%; m.p. 198°C; IR (KBr, cm^{-1}) υ 3520–3601 (OH), 3433, 3351 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.89 (s, 3H, CH_3), 3.91–4.23 (m, 3H, 2H-6', H-5'), 4.41 (m, 2H, H-4', H-3'), 4.44 (t, $J = 9.5$ Hz, 1H, H-2'), 4.51 (s, 1H, 2'-OH), 4.61 (m, 3H, 3'OH, 4'-OH, and 6'-OH), 5.41 (d, 1H, $J_{1'-2'} = 8.27$ Hz, H-1'), 6.83 (s, 2H, NH_2), 6.86 (s, 2H, NH_2), 7.34–7.45 (m, 4H, C_6H_4). ^{13}C NMR: δ 24.3 (CH_3), 60.5 (C-6'), 65.6 (C-4'), 68.3 (C-5'), 70.4 (C-3'), 74.6 (C-2'), 81.1 (C-1'), 94.3 (C-8), 124.3 (Ar-C), 131.3 (2C, Ar-C), 132.5 (2C, Ar-C), 135.7 (Ar-C), 135.3 (C-8a), 152.5 (C-7), 180.2 (C-2), 181.4 (C-4). Anal. Calcd. for $C_{18}H_{22}N_8O_5S$ (462.48): C, 46.75; H, 4.79; N, 24.23; S, 6.93. Found: C, 46.60; H, 4.90; N, 24.10; S, 6.70.

8-(4-Chlorophenyldiazenyl)-4-(β-D-glucopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7d)

Yellow solid (MeOH); yield 75%; m.p. 213°C; IR (KBr, cm^{-1}) υ 3515–3600 (OH), 3456, 3349 (NH_2); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.88–4.16 (m, 3H, 2H-6', H-5'), 4.28 (m, 2H, H-4', H-3'), 4.34 (t, $J = 9.2$ Hz, 1H, H-2'), 4.39 (s, 1H, 2'-OH), 4.52 (m, 3H, 3'OH, 4'-OH, and 6'-OH), 5.35 (d, 1H, $J_{1'-2'} = 9.275$ Hz, H-1'), 6.79 (s, 2H, NH_2), 6.84 (s, 2H, NH_2), 7.33–7.52 (m, 4H, C_6H_4). Anal. Calcd. for $C_{17}H_{19}ClN_8O_5S$ (482.09): C, 42.28; H, 3.97; N, 23.20; S, 6.64. Found: C, 42.10; H, 3.82; N, 23.25; S, 6.52.

8-(4-Bromophenyldiazenyl)-4-(β-D-glucopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7e)

Yellowish white solid (MeOH); yield 75%; m.p. 205°C; IR (KBr, cm^{-1}) υ 3578 (OH), 3431, 3339 (NH_2); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.79–4.01

(m, 3H, 2H-6', H-5'), 4.22 (m, 2H, H-4', H-3'), 4.31 (t, $J = 9.3$ Hz, 1H, H-2'), 4.30 (s, 1H, 2'-OH), 4.42 (m, 3H, 3'OH, 4'-OH, and 6'-OH), 5.24 (d, 1H, $J_{1'-2'} = 7.54$, Hz, H-1'), 6.81 (s, 2H, NH_2), 6.82 (s, 2H, NH_2), 7.33–7.46 (m, 4H, C_6H_4). Anal. Calcd. for $C_{17}H_{19}BrN_8O_5S$ (527.35): C, 38.72; H, 3.63; N, 21.25; S, 6.08. Found: C, 38.60; H, 3.50; N, 21.30; S, 6.28.

4-(β-D-Galactopyranosylthio)-8-(phenyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7f)

Yellowish white solid (MeOH); yield 75%; m.p. 188°C; IR (KBr, cm^{-1}) υ 3574 (OH), 3453, 3382, 3354 (NH_2); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.32 (m, 2H, 2H-6'), 3.52 (m, 1H, H-5'), 3.64 (t, $J_{4'-3'} = 9.6$ Hz, 1H, H-4'), 3.76 (t, $J_{3'-2'} = 9.3$ Hz, $J_{3'-4'} = 9.6$ Hz, 1H, H-3'), 4.12 (t, $J_{2'-1'} =$ 10:2 Hz, $J_{2'-3'} =$ 9:3 Hz, 1H, H-2'), 4.42 (br, D_2O-exchangeable IH, OH), 4.63 (s, br, IH, OH), 4.78 (d, $J_{1'-2'} = 10.35$, 1H, Hz, H-1'), 4.92 (s, br, IH, OH), 5.43 (dd, $J = 5.2$, 7.5 Hz, IH, OH), 6.57 (s, 2H, NH_2), 6.85 (s, 2H, NH_2), 7.34–7.88 (m, 5H, C_6H_5). Anal. Calcd. for $C_{17}H_{20}N_8O_5S$ (448.46): C, 45.53; H, 4.50; N, 24.99; S, 7.15. Found: C, 45.45; H, 4.35; N, 24.88; S, 7.10.

8-(4-Methoxyphenyldiazenyl)-4-(β-D-galactopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7g)

Yellowish white solid (MeOH); yield 75%; m.p. 196°C; IR (KBr, cm^{-1}) υ 3600–3517 (OH), 3453, 3382, 3354 (NH_2); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.34 (s, 3H, OCH_3), 3.41 (m, 2H, 2H-6'), 3.54 (m, 1H, H-5'), 3.65 (t, $J_{4'-3'} = 9.4$ Hz, 1H, H-4'), 3.76 (t, $J_{3'-2'} = 9.2$ Hz, $J_{3'-4'} = 9.5$ Hz, 1H, H-3'), 4.12 (t, $J_{2'-1'} = 10.1$ Hz, $J_{2'-3'} = 9.5$ Hz, 1H, H-2'), 4.52 (s, br, IH, OH), 4.65 (s, br, IH, OH), 4.92 (d, $J_{1'-2'} = 10.35$, 1H, Hz, H-1'), 5.23 (s, br, IH, OH), 5.45 (dd, $J = 5.2$, 7.5 Hz, IH, OH), 6.67 (s, 2H, NH_2), 6.84 (s, 2H, NH_2), 7.33–7.82 (m, 4H, C_6H_4). Anal. Calcd. for $C_{18}H_{22}N_8O_6S$ (478.48): C, 45.18; H, 4.63; N, 23.42; S, 6.70. Found: C, 45.25; H, 4.55; N, 10.42; S, 6.75.

4-(β-D-Galactopyranosylthio)-8-(p-tolyldiazenyl)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7h)

Yellowish white solid (MeOH); yield 75%; m.p. 201°C; IR (KBr, cm^{-1}) υ 3600–3500 (OH), 3443, 3362, 3344 (NH_2); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.95 (s, 3H, CH_3), 3.22 (m, 2H, 2H-6'), 3.36 (m, 1H, H-5'), 3.54 (t, $J_{4'-3'} = 9.6$ Hz, 1H, H-4'), 3.66 (t, $J_{3'-2'} = 9.5$ Hz, $J_{3'-4'} = 9.6$ Hz, 1H, H-3'), 4.00 (t, $J_{2'-1'} = 9.7$ Hz, $J_{2'-3'} = 9.4$ Hz, 1H, H-2'), 4.51 (d, $J_{1'-2'} = 10.35$, 1H, Hz, H-1'), 4.61 (s, br, IH, OH), 4.71 (s, br, IH, OH), 5.42 (s, br, IH, OH), 5.48 (dd, $J = 5.2$, 7.5 Hz, IH, OH), 6.82 (s, 2H, NH_2), 6.89 (s, 2H, NH_2), 7.33–7.54 (m, 4H, C_6H_4). Anal. Calcd. for $C_{18}H_{22}N_8O_5S$ (462.48): C, 46.75; H, 4.79; N, 24.23; S, 6.93. Found: C, 45.20; H, 4.42; N, 10.35; S, 6.68.

8-(4-Chlorophenyldiazenyl)-4-(β-D-galactopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine (7i)

Yellowish white solid (MeOH); yield 75%; m.p. 203°C; IR (KBr, cm^{-1}) υ 3600–3500 (OH), 3465, 3375, 3357 (NH_2), 3129 (CH). ^1H NMR (500 MHz, DMSO-d_6): δ 3.33 (m, 2H, 2H-6'), 3.37 (m, 1H, H-5'), 3.64 (t, $J_{4'-3'} = 9.4$ Hz, 1H, H-4'), 3.68 (t, $J_{3'-2'} = 9.3$ Hz, $J_{3'-4'} = 9.5$ Hz, 1H, H-3'), 4.31 (d, $J_{1'-2'} = 10.35$, 1H, Hz, H-1'), 4.42 (t, $J_{2'-1'} = 9.6$ Hz, $J_{2'-3'} = 9.5$ Hz, 1H, H-2'), 4.65 (t, $J_{OH\text{-}6'} = 5.8$ Hz, 6'-OH), 4.84 (d, $J = 5.5$ Hz, IH, OH), 5.12 (d, $J = 5.2$ Hz, IH, OH), 5.35 (d, $J = 5.4$ Hz, IH, OH), 6.79 (s, 2H, NH_2), 6.87 (s, 2H, NH_2), 7.33–7.56 (m, 4H, C_6H_4). Anal. Calcd. for $C_{17}H_{19}ClN_8O_5S$ (482.90): C, 42.28; H, 3.97; N, 23.20; S, 6.64. Found: C, 42.16; H, 3.84; N, 23.35; S, 6.50.

8-(4-Bromophenyldiazenyl)-4-(β-D-galactopyranosylthio)pyrazolo[1,5-a][1,3,5]triazine-2,7-diamine(7j)

Yellowish white solid (MeOH); yield 75%; m.p. 188°C; ^1H NMR (500 MHz, DMSO-d_6): δ 3.31 (m, 2H, 2H-6'), 3.35 (m, 1H, H-5'), 3.60 (t, $J_{4'-3'} = 9.6$ Hz, 1H, H-4'), 3.62 (t, $J_{3'-2'} = 9.4$ Hz, $J_{3'-4'} = 9.6$ Hz, 1H, H-3'), 4.021 (d, $J_{1'-2'} = 10.35$, 1H, Hz, H-1'), 4.40 (t, $J_{2'-1'} = 9.5$ Hz, $J_{2'-3'} = 9.3$ Hz, 1H, H-2'), 4.55 (t, $J_{OH\text{-}6'} = 5.7$ Hz, 6'-OH), 4.62 (d, $J = 5.8$ Hz, IH, OH), 5.23 (d, $J = 5.5$ Hz, IH, OH), 5.25 (d, $J = 5.2$ Hz, IH, OH), 6.64 (s, 2H, NH_2), 6.82 (s, 2H, NH_2), 7.34–7.48 (m, 4H, C_6H_4). Anal. Calcd. for $C_{17}H_{19}BrN_8O_5S$ (527.35): C, 38.72; H, 3.63; N, 21.25; S, 6.08. Found: C, 38.62; H, 3.75; N, 21.12; S, 6.15.

8-Arylazo-2,7-diamino-4-(methylthio)pyrazolo[1,5-a]-1,3,5-triazines (9a-e)

Method A

A solution of compounds **1a-e** (10 mmol) and dimethyl *N*-cyanodithioiminocarbonate **8** (10 mmol) in DMF (20 mL) was heated at 150°C under microwave 600 W for 10 min. The reaction mixture was monitored by TLC (petroleum ether 60–80 – EtOAc 3:1) until the reactants disappeared. The solvent was then evaporated and the resulting residue was triturated with MeOH to afford compounds **9a-e**, which were recrystallized from the appropriate solvent.

Method B

A solution of compounds **4a-e** (10 mmol) in sodium ethoxide (10 mmol) was refluxed for 30 min and allowed to cool to room temperature; methyl iodide (10 mmol) was then added to the reaction mixture, and refluxed for 3 h. The formed solid product was collected by filtration and recrystallized from the appropriate solvent.

4-Anilino-8-arylazo-2,7-diaminopyrazolo[1,5-a]–1,3,5-triazines (10a-e) [17]

A solution of **6a-j** or **9a-e** (10 mmol) and aniline (10 mmol) in ethanol (20 mL) containing a few drops of triethylamine was refluxed for 3 h, cooled, the precipitate was filtered off, and crystallized from the appropriate solvent.

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