Functionalized 2-Hydrazinobenzothiazole with Isatin and Some Carbohydrates under Conventional and Ultrasound Methods and Their Biological Activities

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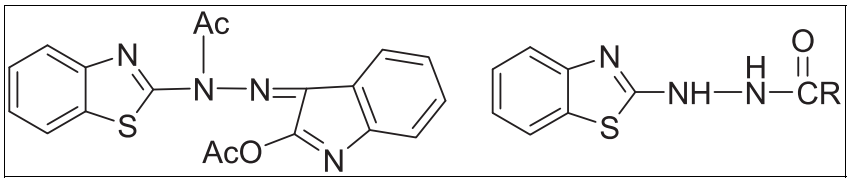

Several chemical reactions were carried out on 3-(benzothiazol-2-yl-hydrazono)-1,3-dihydro-indol-2-one (**2**). 3-(Benzothiazol-2-yl-hydrazono)-1-alkyl-1,3-dihydro-indol-2-one **3a–c** have been achieved. Reaction of compound **2** with ethyl bromoacetate in the presence of K_2CO_3 resulted the uncyclized product **4**. Reaction of compound **2** with benzoyl chloride afforded dibenzoyl derivative **5**. Compound **2** was smoothly acetylated by acetic anhydride in pyridine to give diacetyl derivative **6b**. Moreover, when compound **4** reacted with methyl hydrazine, it yielded dihydrazide derivative **7**, whereas the hydrazinolysis of this compound with hydrazine hydrate gave the monohydrazide derivative **8**. {*N*-(Benzothiazol-2-yl-*N*′-(3-oxo-3,4-dihydro-2*H*-1,2,4-triaza-fluoren-9-ylidene)hydrazino]-acetic acid ethyl ester (**9**) was prepared by ring closure of compound **8** by the action of glacial acetic acid. In addition, the reaction of 2-hydrazinobenzothiazole (**1**) with D-glucose and D-arabinose in the presence of acetic acid yielded the hydrazones **10a**,**b**, respectively. Acetylation of compound **10b** gave compound **11b**. On the other hand, compound **13** was obtained by the reaction of compound **1** with gama-D-galactolactone (**12**). Acetylation of compound **13** with acetic anhydride in pyridin gave the corresponding N^1-acetyl-N^2-(benzothiazolyl)-2-yl)-2,3,4,5,6-penta-*O*-acetyl-D-galacto-hydrazide (**14**). Better yields and shorter reaction times were achieved using ultrasound irradiation. The structural investigation of the new compounds is based on chemical and spectroscopic evidence. Some selected derivatives were studied for their antimicrobial and antiviral activities.

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INTRODUCTION

Considerable attention has been paid in the chemistry of benzothiazole derivatives, which have been studied extensively and were found to have diverse chemical reactivity and broad spectrum of biological activity [1–8]. On the other hand, isatin derivatives were reported to show a variety of biological activities [9–14], such as antibacterial, antifungal, anti-HIV, and anticonvulsant activities. Carbohydrates are important classes of compounds found in many natural and synthetic products with a wide range of pharmaceutical properties [15]. Consequently, the objective of the present study was devoted to the synthesis of functionalized 2-hydrazinobenzothiazole (**1**) with isatin and some carbohydrates to explore their potential antibacterial, antifungal, and antiviral activities. To improve the yields of the isolated products and reduce the reaction times, we decided to use ultrasound irradiation [16] as a nonconventional energy in the synthesis of some selected derivatives.

RESULTS AND DISCUSSION

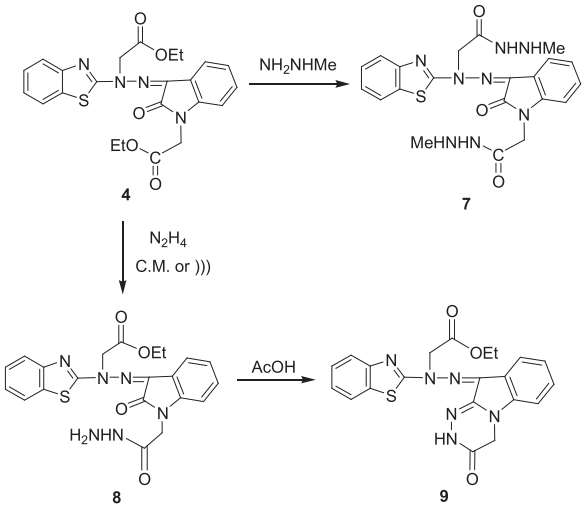
2-Hydrazinobenzothiazole (**1**) can be obtained by irradiation of 2-mercaptobenzothiazole in absolute EtOH and hydrazine hydrate for 30 min. The reaction of compound **1** with isatin in the presence of AcOH under ultrasound irradiation for 10 min resulted the corresponding 3-(benzothiazol-2-yl-hydrazono)-1,3-dihydro-indol-2-one (**2**). A regioselective *N*-alkylation of compound **2** with excess amount of methyl iodide, ethyl iodide, and benzyl chloride has been achieved by using NaH as a base to give the *N*-alkyl derivatives **3a–c**. On the other hand, carbethoxymethylation of **2** with ethyl bromoacetate in the presence of anhydrous K_2CO_3 as catalyst resulted the uncyclized product **4** in 62 % yield within 4.5 h. Improvement of the isolated yield to 74% and significant reduction in the reaction time have been achieved (30 min) under ultrasound irradiation. Spectral analysis proved that carboethoxymethylathion took place at both the nitrogen atoms of isatin ring and hydrazone moiety. *N*-Benzoylation of compound **2** with benzoyl chloride in presence of pyridine gave benzoic acid *N*-benzothiazol-2-yl-*N*′-(1-benzoyl-2-oxo-1,2-dihydro-indol-3-ylidene)hydrazide (**5**). Its IR spectrum showed no absorption band in the range 3140 cm^{-1}, indicating the absence of NH group of hydrazone moiety in addition to bands at 1780.74 and 1721.0 cm^{-1} for two benzoyl groups. ^{13}C NMR spectrum showed two signals at δ_C 167.39 and 168.96 ppm because of two benzoyl groups. Spectral analysis proved that

benzoylation took place at both the nitrogen atoms of isatin ring and hydrazone moiety. Although acetylation of compound **2** with Ac_2O in pyridine did not afford the expected product **6a**, the isolated product was compound **6b**, and its structure was assigned on the basis of the spectral characteristics. The IR spectrum of the product showed no absorption for an amide group and showed absorption bands at 1735.40 and 1705.06 cm^{-1} because of OAc and NAc groups, respectively. ^1H NMR spectrum showed two singlets for six protons because of two acetyl groups, at δ_H 2.67 and 4.57 ppm. Attempted deacetylation of **6b** with aqueous solution of NaOH and subsequent acidification with acetic acid gave a product identical with compound **2** (Scheme 1).

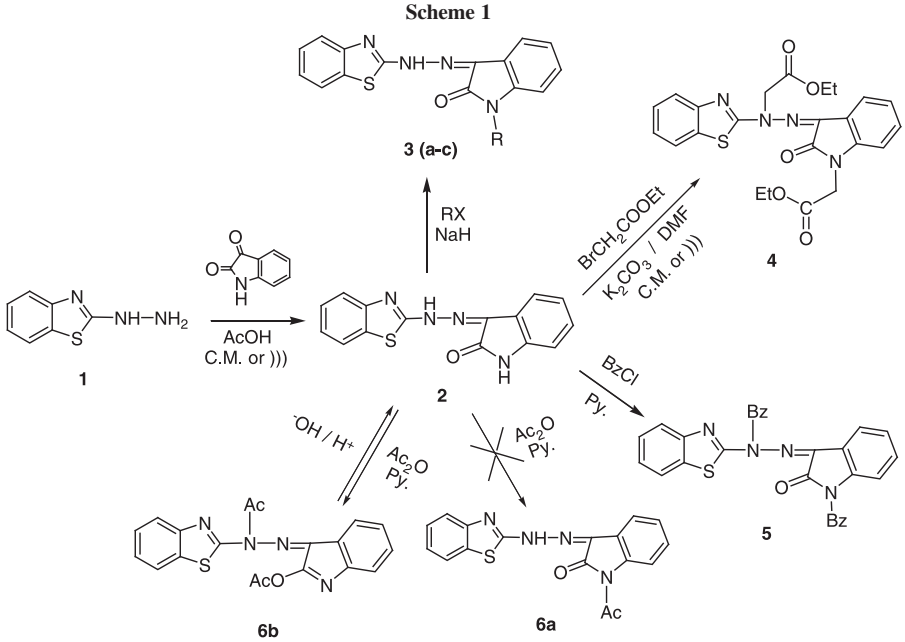
Reaction of compound **4** with methyl hydrazine gave the corresponding dihydrazide, {*N*-(benzothiazol-2-yl-*N*′-[1-(*N*′-methylhydrazinocarbonylmethyl)-2-oxo-1,2-dihydro-indol-3-ylidene]-hydrazino}-acetic acid *N*′-methylhydrazide (**7**). Its IR spectrum showed no absorption bands in the range 1700 cm^{-1}, indicating the absence of ester carbonyl groups. The ^1H NMR spectrum showed two singlet signals at δ_H 2.98 and 3.08 ppm because of two CH_3 groups. On the other hand, nucleophilic attack of hydrazine on the carbonyl-ester of **4** has been proceeded by ultrasound irradiation for 15 min to afford the corresponding monohydrazide, {*N*-(benzothiazol-2-yl-*N*′-[1-(*N*′-methylhydrazinocarbonylmethyl)-2-oxo-1,2-dihydro-indol-3-ylidene]hydrazino}-acetic acid ethyl ester (**8**) instead of dihydrazide in 91% yield; conventional heating required 5 h to give 78% yield. Its IR spectrum showed a band of carbonyl-ester at 1719.37 cm^{-1} and a band at 3307.93 cm^{-1} for NH group. The functionalized in compound **8** made a valuable key precursor for the formation of fused heterocyclic compound. Thus, treatment of compound **8** with glacial AcOH afforded {*N*-(benzothiazol-2-yl-*N*′-(3-oxo-3,4-dihydro-2*H*-1,2,4-triaza-fluoren-9-ylidene)hydrazino]-acetic acid ethyl ester (**9**) in 94% yield (Scheme 2).

The reaction of 2-hydrazinobenzothiazole (**1**) with equimolar amounts of a number of monosaccharides in an aqueous ethanolic solution and in the presence of a catalytic amount of glacial AcOH were performed either under conventional

Scheme 2



Scheme 1



a : R= Me, X= I, **b:** R= Et, X= I, **c:** R= Bn, X= Cl.

heating or under ultrasound irradiation. The hydrazones **10a**,**b** could be prepared from the monosaccharides D-glucose and D-arabinose, respectively. The arylidene derivatives **10a**,**b** were characterized by the absence of an NH band in their IR spectra and by the presence of the arylidene proton NCH signal in the ^{1}H NMR spectra. When the reactions were carried out under ultrasound irradiation, 10 min was required to give higher yield with higher purity. Treatment of compound **10b** with Ac_2O in pyridine at 0°C gave colorless crystalline product **11b**, whose combustion analysis indicated that preacetylation had taken place on both the polyol residue and on NH groups. Alternatively, compound **13** could be obtained in 86% yield by ultrasound irradiation of a mixture of compound **1** in EtOH with gama-D-galactolactone (**12**) in the presence of glacial AcOH for 5 min; conventional heating required 7 h to give 71% yield. Acetylation of compound **13** with Ac_2O in pyridin gave the corresponding N^1-acetyl-N^2-(benzothiazolyl)-2-yl)-2,3,4,5,6-penta-*O*-acetyl-D-galacto-hydrazide (**14**); the acetylation took place on the N-atom of the hydrazide group in addition to the polyol residue (Scheme 3).

Table 1 shows that when using ultrasound irradiation in the synthesis of some selected derivatives (**1**, **2**, **4**, **8**, **10a**,**b**, and **13**), the reactions need shorter time (5–30 min) to be completed and give higher product yields (72–99%) with higher purity compared with conventional methods.

Biological activity. Biological activity tests were performed at the Biotechnology lab of Egyptian Petroleum Research Institute, Cairo, Egypt.

Antimicrobial activity. Compounds **2–5**, **6b**, **8**, **10a**,**b**, **13**, and **14** were screened for their *in vitro* antibacterial and antifungal activity. The antibacterial activity of these compounds were tested against two Gram positive bacteria (*Bacillus pumilus*, NCTC8214, and *Micrococcus luteus*, ATCC-25922) and two Gram negative bacteria (*Pseudomonas aeruginosa*, ATCC10145, and *Sarcina lutea*, ATCC-9341) and antifungal activities against two fungi (*Penicillium crysogenum* and *Candida albicans* IMRU3669) by disc diffusion method at 5 mg/mL disc concentration [17,18]. DMF is used as solvent control. The bacteria and fungi were maintained on nutrient agar and Czapek's Dox agar medium, respectively. The results are measured in millimeter (mm). Ampicillin trihydrate was used as a standard drug against Gram positive and Gram negative bacteria. Against fungi, Ketoconazole was used as a standard drug.

For antibacterial activity, most of the tested compounds were found to possess various antibacterial activities (Table 2 and Fig. 1). The tested compounds are more active against Gram positive than the Gram negative bacteria. Compound **2** was the most active derivative giving the best antibacterial activity against *M. luteus* and *S. lutea* compared with ampicillin trihydrate. Furthermore, the antibacterial activities of compounds **3a** and **3c** against *M. luteus* were higher than ampicillin trihydrate.

Table 1

Synthesis of some derivatives under both ultrasound irradiation and conventional methods.

	Ultrasound		Conventional	
Compounds	Time (min)	% Yield	Time (h)	% Yield
1	30	99	5	92
2	10	94	3	78
4	30	74	4.5	62
8	15	91	5	78
10a	10	84	3	70
10b	10	72	8	55
13	5	86	7	71

Scheme 3

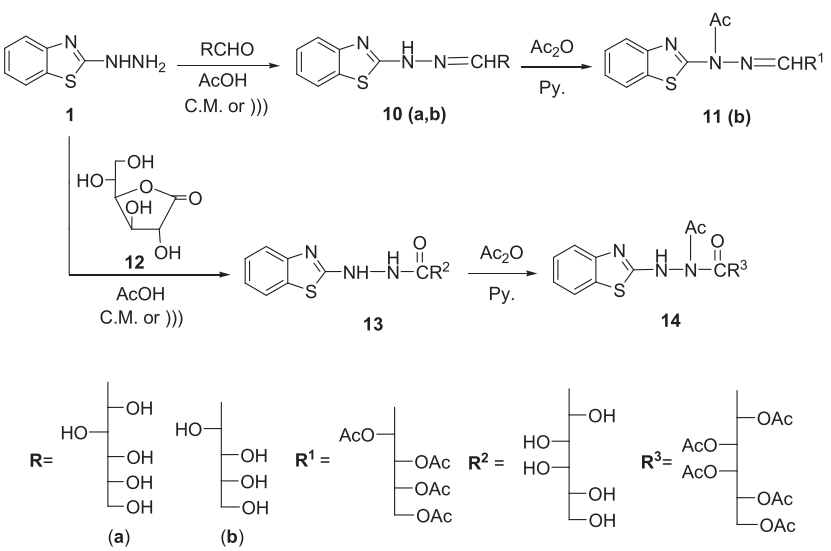


Table 2

Antimicrobial screen of the tested compound.

Tested compounds	Mean values of inhibition zones (mm)					
	Bacillus pumilus	*Micrococcus luteus*	*Pseudomonas aeruginosa*	*Sarcina lutea*	*Peneicillium*	*Candida*
2	14.0	32.0	12.0	35.0	18.0	—
3a	15.0	26.0	13.0	28.0	14.0	13.0
3b	16.0	18.0	—	17.0	14.0	—
3c	14.0	27.0	14.0	28.0	15.0	13.0
4	15.0	12.0	—	—	14.0	—
5	13.0	12.0	—	—	—	—
6b	14.0	14.0	—	19.0	14.0	—
8	—	—	13.0	—	—	13.0
10a	15.0	12.0	—	12.0	15.0	12.0
10b	15.0	13.0	—	—	16.0	13.0
13	16.0	13.0	—	—	14.0	14.0
14	16.0	13.0	—	—	18.0	—
Amp.[a]	34.0	25.0	29.0	30.0	—	—
Ket.[b]	—	—	—	—	21.0	24.0

[a]Amp. = ampicillin trihydrate.
[b]Ket. = ketoconazole.

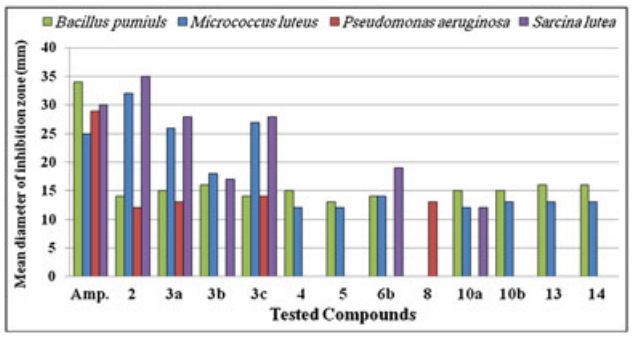


Figure 1. Antibacterial screen of the tested compounds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Also, most of the tested compounds were found to possess various antifungal activities toward fungi (Table 2 and Fig. 2). Compounds **2**, **10b**, and **14** were found to possess higher antifungal activity compared with other derivatives.

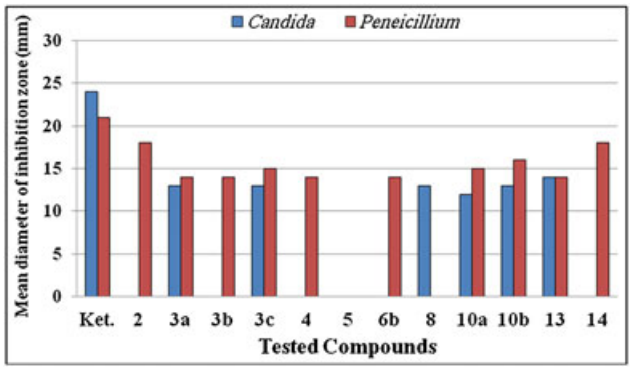


Figure 2. Antifungal screen of the tested compounds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

However, the activities of the tested compounds are less than those of Ketoconazole.

Antiviral activity. The antiviral activity of compounds **2–5**, **4b**, **8**, **10a**,**b**, **13**, and **14** was tested against Coxsackie B4 (Cox B4), Herpes simplex (HSV-1), and Hepatitis A (HAV) viruses using plaque assay [19]. All tested samples showed less than 10% effect which is not considered as a good result (not antiviral candidates).

EXPERIMENTAL

Commercially available solvents and reagents were purified according to the standard procedures. All melting points were measured on a Mel-Temp apparatus (Dubuque, IA) and are uncorrected. Thin layer chromatography (TLC) was performed on aluminum silica gel 60 F_{254} (E-Merk). The spots were detected by iodine and UV light absorption. IR spectra were recorded for the compounds in a FTIR, Perkin Elmer SP 100 Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker WM 400 and 600 MHz spectrometers using TMS or the signal of the deuterated solvent was used as internal standard. Chemical shifts (δ) are given in ppm relative to the signal for TMS as standard and coupling constants in Hz. The reactions that were carried out by ultrasound irradiation were performed using Daihan (Wiseclean, D-400H) ultrasonic bath. Microanalysis was performed by Perkin Elmer elemental analyzer at the Faculty of Science, King Abdul Aziz University.

2-Hydrazinobenzothiazole (1)

Method A. A solution of 2-mercaptobenzothiazole (3.0 g, 17.9 mmol) in absolute EtOH (60 mL) was treated with hydrazine hydrate (10 mL). The reaction mixture was refluxed on water bath for 5 h. The mixture was cooled and the solvent was evaporated *in vacuo*. The separated product was filtered and crystallized from EtOH to give pale yellow crystals (2.70 g, 92% yield); m.p. 194°C [lit. [20], m.p. 189–194°C].

Method B. A solution of 2-mercaptobenzothiazole (3.0 g, 17.9 mmol) in absolute EtOH (60 mL) was treated with hydrazine hydrate (10 mL). The reaction mixture was sonicated at a frequency of 40 kHz for 30 min at 45°C. The mixture was cooled, and the solvent was evaporated *in vacuo*. The separated product was filtered and crystallized from EtOH to give an identical product with the product that was obtained from method **A** (2.92 g, 99% yield); m.p. 194–196°C.

3-(Benzothiazol-2-yl-hydrazono)-1,3-dihydro-indol-2-one (2)

Method A. A solution of 2-hydrazinobenzothiazole (**1**) (1.0 g, 6.05 mmol) in a mixture of EtOH–DMF (1:1) (50 mL) was treated with isatin (0.89 g, 6.05 mmol) in absolute EtOH (30 mL) and AcOH (5 drops). The reaction mixture was heated under reflux for 3 h. The product that separated out was filtered off, dried, and crystallized from EtOH to give deep orange crystals (1.39 g, 78% yield); m.p. 312°C [lit. [21], m.p. 276–278°C]. FTIR: 1626.51 (CN), 1692.58 (OCN), and 3141.90 cm^{-1} (NH). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 6.98 (d, 1H, J = 7.2 Hz, isatin, C_7—H); 7.12, 7.28 (2t, each 1H, J = 7.5 Hz, isatin, $C_{5,6}$—H); 7.37, 7.42 (2t, each 1H, J = 7.7 Hz, benzothiazole, $C_{5,6}$—H); 7.56 (d, 1H, J = 7.8 Hz, isatin, C_4—H); 7.65 (d, 1H, J = 7.2 Hz, benzothiazole, C_4—H); 7.96 (d, 1H, J = 7.8 Hz, benzothiazole, C_7—H); 11.30, 13.40 (2s, 2H, D_2O exchangeable, 2 NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 111.05, 119.46, 119.98, 120.44, 121.91, 122.40, 123.26, 126.34, 130.70, 133.39, 141.42 (Ar—C); 141.59 (CN, indol); 151.26 (CO); 165.44 (CN, thiazole). *Anal*. Calcd for $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04%. Found: C, 61.68; H, 3.05; N, 18.58%.

Method B. A solution of 2-hydrazinobenzothiazole (**1**) (2.0 g, 12.10 mmol) in a mixture of EtOH–DMF (1:1) (90 mL) was treated with isatin (1.78 g, 12.10 mmol) in EtOH (60 mL) and AcOH (0.5 mL). The reaction mixture was sonicated at a frequency of 40 kHz for 10 min at 40°C and processed as before to give compound **2** (3.34 g, 94% yield); m.p. 312–314°C. IR and ^{1}H NMR spectra were superimposable with the spectra from method **A**.

3-(Benzothiazol-2-yl-hydrazono)-1-methyl-1,3-dihydro-indol-2-one (3a). A solution of compound **2** (0.59 g, 2.0 mmol) and NaH (0.10 g, 4.17 mmol) in a mixture of EtOH–DMF (10:1) (100 mL) was heated under reflux for 4 h. Then, methyl iodide (0.27 mL, 4.34 mmol) was added, and the mixture was reflux for additional 14 h. The product that separated out was filtered off, dried, and crystallized from EtOH–DMF to give deep orange crystals (0.54 g, 87% yield); m.p. 296°C, $\mathbf{R_f}$: 0.49 (EtAc–*n*-hexane, 1:3). FTIR: 3181.77 (NH), 1695.38 (OCN), and 1626.0 cm^{-1} (CN). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 3.83 (s, 3H, CH_3); 6.87 (d, 1H, J = 7.8 Hz, indol, C_4—H); 6.82 (d, 1H, J = 7.8 Hz, indol, C_7—H); 7.05, 7.12 (2t, each 1H, J = 7.8 Hz, indol, $C_{5,6}$—H); 7.31, 7.46 (2t, each 1H, J = 7.8 Hz, benzothiazole, $C_{5,6}$—H); 7.81 (d, 1H, J = 7.8 Hz, benzothiazole, C_4—H); 8.30 (d, 1H, J = 7.2 Hz, benzothiazole, C_7—H); 13.42 (bs, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 31.91 (CH_3); 109.92, 117.72, 120.15, 120.59, 121.49, 121.85, 123.98, 126.50, 127.31, 131.22, 141.75, 142.92 (Ar—C); 140.43 (CN, indol); 143.02 (CO); 165.39 (CN, thiazol). *Anal*. Calcd for $C_{16}H_{12}N_4OS$ (308.36): C, 62.32; H, 3.92; N, 18.17%. Found: C, 62.75; H, 4.35; N, 17.98%.

3-(Benzothiazol-2-yl-hydrazono)-1-ethyl-1,3-dihydro-indol-2-one (3b). A solution of compound **2** (0.59 g, 2.0 mmol) and NaH (0.10 g, 4.17 mmol) in a mixture of EtOH–DMF (10:1) (100 mL) was heated to 100°C for 4 h. Then, ethyl iodide (0.41 mL, 5.05 mmol) was added, and the mixture was allowed under reflux for 5.5 h. The obtained product was filtered off, dried, and crystallized from EtOH to give orange crystals (0.55 g, 85% yield); m.p. 278°C, $\mathbf{R_f}$: 0.38 (EtAc–*n*-hexane, 1:3). FTIR: 3183.0 (NH), 1693.23 (OCN), and 1620.6 cm^{-1} (CN). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 1.38 (t, 3H, J = 7.2, CH_3); 4.39 (q, 2H, CH_2); 6.79 (d, 1H, J = 7.8 Hz, indol, C_7—H); 6.86 (d, 1H, J = 7.8 Hz, indol, C_4—H); 7.03, 7.35 (2t, each 1H, J = 7.8 Hz, indol, $C_{5,6}$—H); 7.29, 7.44 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{5,6}$—H); 7.81 (d, 1H, J = 7.2 Hz, benzothiazole, C_4—H); 8.23 (d, 1H, J = 7.2 Hz, benzothiazole, C_7—H); 13.4 (bs, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 12.11 (CH_3); 40.20 (CH_2); 110.03, 117.78, 121.55, 121.88, 123.18, 123.25, 124.24, 126.97, 127.08, 131.27, 139.39, 142.96 (Ar—C); 139.39 (CN, indol); 143.06 (CO); 165.35 (CN, thiazol). *Anal*. Calcd for $C_{17}H_{14}N_4OS$ (322.38): C, 63.33; H, 4.38; N, 17.38%. Found: C, 62.87; H, 3.95; N, 16.93%.

3-(Benzothiazol-2-yl-hydrazono)-1-benzyl-1,3-dihydro-indol-2-one (3c). A solution of **2** (0.59 g, 2.0 mmol) and NaH (0.10 g, 4.17 mmol) in a mixture of EtOH–DMF (10:1) (100 mL) was heated under reflux for 4 h. Benzyl chloride (0.5 mL, 4.33 mmol) was added, and the mixture was reflux for additional 16 h. The product that separated out was filtered off, dried, and crystallized from EtOH to give deep yellow crystals (0.58 g, 74% yield); m.p. 300°C, $\mathbf{R_f}$: 0.67 (EtAc–*n*-hexane, 1:3). FTIR: str. 3140.87 (NH), 1693.27 (OCN), and 1627 cm^{-1} (CN). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 2.09 (s, 2H, N—CH_2); 6.97 (d, 1H, J = 7.8 Hz, indol, C_7—H); 7.10, 7.25 (2t, each 1H, J = 8.4 Hz, indol, $C_{5,6}$—H); 7.34, 7.39 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{5,6}$—H); 7.54 (d, 1H, J = 7.2 Hz, indol, C_4—H); 7.54 (d, 1H, J = 7.2 Hz, benzothiazole, C_4—H); 7.65 (d, 1H, J = 7.8 Hz, benzothiazole, C_7—H); 6.85–8.28 (m, 5H, Ar—H); 13.89 (bs, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 31.26 (CH_2); 111.78, 117.45, 120.79, 122.62, 123.01, 123.35, 124.23, 127.23, 128.50, 131.02, 131.71 (Ar—C); 138.93 (CN, indole); 141.96 (CN, thiol); 208.74 (CO). *Anal*. Calcd for $C_{22}H_{16}N_4OS$ (384.45): C, 68.73; H, 4.19; N, 14.57%. Found: C, 68.91; H, 4.28; N, 14.25%.

[*N*-Benzothiazol-2-yl-*N′*-(1-ethoxycarbonylmethyl-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazino]acetic acid ethyl ester (4)

Method A. To a solution of compound **2** (1.0 g, 3.40 mmol) in a mixture of EtOH–DMF (1:1) (100 mL), anhydrous K_2CO_3 (0.7 g, 5.06 mmol) was added. The mixture was heated under reflux for 2.5 h, cooled, and then treated with ethyl bromoacetate (1.13 mL, 10.19 mmol). The reaction mixture was heated under reflux for 4.5 h. It was poured onto crushed ice. and the product that separated out was filtered off, washed with water, and dried. It was crystallized from EtOH to give yellow crystals (0.98 g, 62% yield); m.p. = 276°C, $\mathbf{R_f}$: 0.16 (EtAc–*n*-hexane, 1:3). FTIR: 1620.08 (OCN); 1725.02 and 1743.33 cm^{-1} (COOEt). ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 1.61, 1.64 (2t, 6H, 2 CH_3); 4.28, 4.29 (2q, 4H, 2 CH_2CH_3); 5.01 (s, 2H, N—CH_2); 5.10 (s, 2H, N—CH_2, indol); 6.87 (d, 1H, J = 7.8 Hz, isatin, C_7—H); 7.08,7.24 (2t, each 1H, J = 7.2 Hz, isatin, $C_{5,6}$—H); 7.27, 7.37 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{5,6}$—H); 7.58 (d, 1H, J = 7.2 Hz, isatin, C_4—H); 7.70 (d, 1H, J = 7.2 Hz, benzothiazole, C_4—H); 8.20 (d, 1H, J = 7.2 Hz, benzothiazole C_7—H). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 14.11, 14.22 (2 CH_3); 45.91, 46.04 (2 CH_2COO); 62.10, 62.20 (2 CH_2CH_3); 109.68, 116.43, 118.42, 121.25, 122.46, 123.01, 126.69, 127.79, 130.50, 131.15, 141.56, 143.74 (Ar—C); 139.39 (CN, indol); 159.43 (CO, indol); 166.69

(CN, thiazol); 166.12, 166.28 (2 COO). *Anal.* Calcd for $C_{23}H_{22}N_4O_5S$ (466.51): C, 59.22; H, 4.75; N, 12.01%. Found: C, 59.23; H, 4.26; N, 12.27%.

Method B. A solution of compound **2** (0.65 g, 2.21 mmol) in a mixture of EtOH–DMF (1:1) (60 mL) was treated with ethyl bromoacetate (0.75 mL, 6.76 mmol) and anhydrous K_2CO_3 (0.5 g, 3.62 mmol). The reaction mixture was sonicated at a frequency of 40 kHz for 30 min at 40°C and processed as before to give compound **4** (0.76 g, 74% yield); m.p. 273–274°C. IR and ^{1}H NMR spectra were superimposable with the spectra from method **A**.

Benzoic acid *N*-benzothiazol-2-yl-*N′*-(1-benzoyl-2-oxo-1,2-dihydro-indol-3-ylidene)hydrazide (5). A solution of **2** (0.8 g, 2.72 mmol) in dry pyridine (12 mL) was cooled in an ice bath, then treated with benzoyl chlorid (12 mL) with stirring. The mixture was kept at rt overnight; it was poured onto crushed ice. The product that separated out was filtered off, washed repeatedly with water, dried, and crystallized from EtOH to give orange crystals (1.29 g, 94% yield); m.p. 261–263°C, $\mathbf{R_f}$: 0.65 (EtAc–*n*-hexane, 1:3). FTIR: 1780.74, 1721.17 (CO—Ph), 1692.59 (OCN), and 1597.14 cm^{-1} (CN). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 7.32–8.57 (m, 18H, Ar—H). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 114.47, 115.21, 119.69, 119.75, 123.06, 123.19, 126.70, 127.11, 128.09, 128.21, 128.55, 128.65, 129.33, 129.49, 129.76, 130.74, 132.58, 132.97 (Ar—C); 132.97 (CN, indol); 134.62 (CO, indol); 163.02 (CN, thiazol); 167.39, 168.96 (2COPh). *Anal.* Calcd for $C_{29}H_{18}N_4O_3S$ (502.54): C, 69.31; H, 3.61; N, 11.15%. Found: C, 68.28; H, 3.68; N, 11.10%.

Acetic acid 3-(*N*-acetyl-*N*'-benzothiazol-2-yl-hydrazono)-3*H*-indol-2-yl ester (6b). A solution of compound **2** (0.8 g, 2.72 mmol) in dry pyridine (12 mL) was cooled in an ice bath, then treated with Ac_2O (12 mL) with stirring for 2 h. The mixture was kept at rt overnight, then poured onto crushed ice. The product that separated out was filtered off, washed repeatedly with water, dried, and crystallized from EtOH to give orange crystals (1.0 g, 97% yield); m.p. 208–210°C, $\mathbf{R_f}$: 0.71 (EtAc–*n*-hexane, 1:3). FTIR: 1735.40 (OAc), 1705.06 (NAc), and 1604.83 cm^{-1} (CN). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 2.67 (s, 3H, OAc), 4.57 (s, 3H, NAc), 7.19–8.17 (m, 8H, Ar—H). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 26.46, 26.60 (2 CH_3); 113.05, 115.81, 116.50, 119.31, 119.41, 123.13, 123.29, 123.90, 124.82, 126.14, 126.89, 127.21 (Ar—C); 130.59, 139.65 (CN, indole); 163.96 (CN, thiazole); 170.61 (CH_3COO); 176.07 (CH_3CON). *Anal.* Calcd for $C_{19}H_{14}N_4O_3S$ (378.40): C, 60.31; H, 3.73; N, 14.81%. Found: C, 60.27; H, 3.60; N, 14.60%.

Effect of alkali on compound 6b. A solution of **6b** (0.1 g, 0.26 mmol) and NaOH (0.11 g, 2.75 mmol) in H_2O–EtOH (1:1) (10 mL) was boiled under reflux for 4 h. The mixture was cooled and acidified with AcOH. The product that separated out was filtered off and crystallized from EtOH to give deep orange crystals (0.08 g, 88% yield); m.p. 308–310°C. IR spectra were superimposable with the spectra of compound **2**.

{*N*-(Benzothiazol-2-yl-*N′*-[1-(*N′*-methylhydrazinocarbonyl-methyl)-2-oxo-1,2-dihydro-indol-3-ylidene]-hydrazino}-acetic acid *N′*-methylhydrazide (7). A solution of compound **4** (0.4 g, 0.85 mmol) in EtOH (40 mL) was treated with methyl hydrazine (1.0 mL, 19.1 mmol). The reaction mixture was heated under reflux for 14 h. The solvent was evaporated *in vacuo*, and the residue was treated with warm acetone. The separated product was filtered, dried, and crystallized from EtOH to give deep orange crystals (0.25 g, 63% yield); m.p. 105–108°C, $\mathbf{R_f}$: 0.16 (EtAc–*n*-hexane, 1:3). FTIR: 3422.02 (NH) and 1620.08 cm^{-1} (OCN). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 2.98, 3.08 (2s, 6H, 2CH_3); 4.35 (s, 2H, NCH_2); 4.49 (s, 2H, NCH_2, indol); 6.80–7.84 (m, 8H, Ar—H); 8.30 (bs, 4H, D_2O exchangeable, 4NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 30.87 (2CH_3); 42.58 (CH_2N–thiazol); 61.34 (CH_2N–indol); 127.13, 127.35, 127.49, 128.08, 128.48, 129.14, 130.30, 130.63, 130.75 (Ar—C); 143.53 (CO, indol); 169.92 (CN); 184.09, 184.49 (2CONH). *Anal.* Calcd for $C_{21}H_{22}N_8O_3S$ (466.52): C, 54.07; H, 4.75; N, 24.02%. Found: C, 54.47; H, 4.92; N, 23.43%.

{*N*-(Benzothiazol-2-yl-*N′*-[1-(*N′*-methylhydrazinocarbonyl-methyl)-2-oxo-1,2-dihydro-indol-3-ylidene]hydrazino}-acetic acid ethyl ester (8)

Method A. Hydrazine hydrate (1.0 mL) was added to a solution of compound **4** (0.37 g, 0.79 mmol) in absolute EtOH (40 mL). The mixture was heated under reflux for 5 h. The solid mass, which separated out upon cooling, was filtered, dried, and recrystallized from EtOH–DMF in deep orange crystals (0.28 g, 78% yield); m.p. 296°C, $\mathbf{R_f}$: 0.71 (EtAc–*n*-hexane, 1:1). FTIR: 3307.93 (N—H); 1719.37 (COOEt); 1678.23 and 1650.8 cm^{-1} (OCN). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.23 (t, 3H, J = 9.54, CH_3CH_2); 4.20 (q, 2H, CH_2CH_3); 5.15 (s, 2H, CH_2–indol); 5.21 (s, 2H, NCH_2); 6.86 (d, 1H, J = 7.3 Hz, isatin, C_7—H); 7.02 (t, 1H, J = 7.3 Hz, isatin, C_5—H); 7.29 (m, 2H, benzothiazole, C_6—H + isatin, C_6—H); 7.44 (t, 1H, J = 7.2 Hz, benzothiazole, C_5—H); 7.64 (d, 1H, J = 8.2 Hz, benzothiazole, C_4—H); 7.83 (d, 1H, J = 7.8 Hz, isatin, C_4—H); 8.11 (d, 1H, J = 6.72 Hz, benzothiazole, C_7—H); 10.62 (bs, 3H, D_2O exchangeable, $NHNH_2$). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 39.80 (CH_3); 39.91 (CH_2CONH); 40.03 (CH_2COO); 45.92 (CH_2CH_3); 109.93, 111.79, 117.62, 120.11, 121.50, 121.97, 122.95, 123.76, 126.83, 127.60 (Ar—C); 131.36 (CN, indol); 162.05 (CN, thiazol); 165.33 (CO, indol); 165.35 ($CONH_2NH_2$); 173.04 (COO). *Anal.* Calcd for $C_{21}H_{20}N_6O_4S$ (452.49): C, 55.74; H, 4.46; N, 18.57%. Found: C, 55.47; H, 3.97; N, 18.26%.

Method B. Hydrazine hydrate (1.0 mL) was added to a solution of compound **4** (0.35 g, 0.75 mmol) in absolute EtOH (40 mL). The reaction mixture was sonicated at a frequency of 40 kHz for 15 min at 40°C and processed as before to give compound **8** (0.31 g, 91% yield); m.p. 293–295°C.

{*N*-(Benzothiazol-2-yl-*N′*-(3-oxo-3,4-dihydro-2*H*-1,2,4-triaza-fluoren-9-ylidene)hydrazino]-acetic acid ethyl ester (9). A solution of compound **8** (0.1 g, 0.22 mmol) in glacial AcOH (6 mL) was heated under reflux for 5 h. The mixture was poured onto crushed ice. The product was crystallized from EtOH–DMF to give yellow crystals (0.09 g, 94% yield); m.p. 316°C, $\mathbf{R_f}$: 0.67 (EtAc–*n*-hexane, 1:3). FTIR: 1708.98 (COO), 1670.04 (OCN), 1611.08 (CN), and 3184.87 cm^{-1} (NH). ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 1.83 (t, 3H, CH_3CH_2); 4.45 (q, 2H, CH_2CH_3); 5.01 (s, 2H, CH_2–indol); 5.13 (s, 2H, N—CH_2); 6.82 (d, 1H, J = 7.8 Hz, isatin C_7—H); 7.01, 7.23 (2t, 2H, J = 7.2 Hz, isatin $C_{5,6}$—H); 7.28, 7.38 (2t, 2H, J = 7.2 Hz, benzothiazole $C_{5,6}$—H); 7.47 (d, 1H, J = 8.4 Hz, benzothiazole C_4—H); 7.77 (d, 1H, J = 7.8 Hz, isatin C_4—H); 8.22 (d, 1H, J = 7.8 Hz, benzothiazole C_7—H); 10.60 (bs, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 39.79 (CH_3); 39.91 (CH_2CONH); 40.03 (CH_2COO); 45.68 (CH_2CH_3); 109.85, 110.10, 111.79, 117.62, 121.50, 122.14, 122.98, 123.67, 126.86, 127.94 (Ar—C); 131.38 (CN, indol); 143.75 (CN, triazin), 164.46 (CN, thiazol); 165.35 (CONH); 173.01 (COO). *Anal.* Calcd for $C_{21}H_{18}N_6O_3S$ (434.47): C, 58.05; H, 4.18; N, 19.34%. Found: C, 58.24; H, 4.35; N, 19.84%.

Sugar (benzothiazol-2-yl)hydrazones

Method A. A solution of 2-hydrazinobenzothiazole (**1**) (0.46 g, 2.78 mmol) in a mixture of EtOH–DMF (1:1) (45 mL) was added to a solution of the appropriate monosaccharide (2.78 mmol) in small amount of H_2O and AcOH (3 drops). The reaction mixture was heated on a boiling water bath from 3 to 8 h. The solvent was evaporated *in vacuo*, and the solid mass which separated out was filtered off, washed with water, and crystallized from EtOH to give colorless crystals.

Method B. A solution of 2-hydrazinobenzothiazole (**1**) (0.46 g, 2.78 mmol) in a mixture of EtOH–DMF (1:1) (45 mL) was added to a solution of the appropriate monosaccharide (2.78 mmol) in small amount of H_2O and AcOH (3 drops). The reaction mixture was sonicated at a frequency of 40 kHz for 10 min at rt. Then, the solvent was evaporated *in vacuo*. The product that separated out was filtered, washed with water, and crystallized from EtOH to give colorless crystals.

D-Glucose (benzothiazol-2-yl)hydrazone (10a). From method **A**: (0.64 g, 70% yield); from method B: (0.76 g, 84% yield); m.p. 167–168°C, $\mathbf{R_f}$: 0.71 (EtAc–MeOH, 1:1). FTIR: 3400 (OH) and 1561.91 cm^{-1} (CN). ^1H NMR (600 MHz, DMSO-d_6): δ_H = 2.97, 3.04, 3.13, 3.19 (4m, 4H, H-6″, 6′, 5′ and H-4′); 3.67 (t, 1H, J = 9.6 Hz, H-3′); 3.86 (t, 1H, J = 9 Hz, H-2′); 4.55, 4.89, 4.97, 5.02, 6.17 (5d, 5H, D_2O exchangeable, 5OH); 7.01, 7.22 (2t, each 1H, J = 6.6 Hz, benzothiazole, $C_{5,6}$—H); 7.34 (d, 1H, J = 7.8 Hz, benzothiazole, C_4—H); 7.71 (d, 1H, J = 7.2 Hz, benzothiazole, C_7—H); 9.29 (s, 1H, HCN); 10.25 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 62.05 (CH_2); 71.02 (C-5); 72.23 (C-4); 74.68 (C-3); 77.60 (C-2); 117.99, 120.50, 120.90, 125.20, 130.53, 153.10 (Ar—C + CH); 172.84 (CN, thiazol). *Anal*. Calcd for $C_{13}H_{17}N_3O_5S$ (327.36): C, 47.70; H, 5.23; N, 12.84%. Found: C, 47.10; H, 4.94; N, 12.32%.

D-Arabinose (benzothiazol-2-yl)hydrazone (10b). From method A: (0.45 g, 55% yield); from method B: (0.59 g, 72% yield); m.p. 201–202°C, $\mathbf{R_f}$: 0.83 (EtAc–MeOH, 1:1). FTIR: 3440 (OH), 3112.53 (str., NH), 1606.37 (CN), and 1574.91 cm^{-1} (bend., NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H = 4.38 (m, 1H, H-4′); 4.45, 4.53, 4.54, 4.84 (4d, 4H, D_2O exchangeable, 4OH); 4.61, 4.64 (2dd, 2H, H-5′, H-5″); 4.72 (t, 1H, H-2′); 4.87 (dd, 1H, H-3′); 7.09, 7.38 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{6,5}$—H); 7.49 (d, 1H, J = 6.8 Hz, benzothiazole, C_4—H); 7.75 (d, 1H, J = 6.8 Hz, benzothiazole, C_7—H); 7.70 (d, 1H, HCN); 11.89 (bs, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 63.41 (CH_2); 70.14 (C-4); 70.92 (C-3); 73.51 (C-2); 120.71, 121.01, 121.41, 121.48, 125.52, 125.89 (Ar—C + CH); 167.05 (CN, thiazol). *Anal*. Calcd for $C_{12}H_{15}N_3O_4S$ (297.33): C, 48.47; H, 5.08; N, 14.13%. Found: C, 48.28; H, 4.92; N, 13.66%.

2,3,4,5-Tetra-*O*-acetyl-D-arabino-N^2-acetyl-N^2-(benzothiazol-2-yl) hydrazone (11b). A solution of compound **10b** (0.5 g, 1.68 mmol) in dry pyridine (10 mL) was cooled in ice bath, then treated with Ac_2O (10 mL) with stirring. The mixture was kept at 18–20°C overnight, then poured onto crushed ice. The product was extracted with CH_2Cl_2 (2 × 20 mL), and the solvent was evaporated under reduced pressure. The product that separated out was filtered, dried, and crystallized from $CHCl_3$ as colorless needles (0.52 g, 61% yield); m.p. 126–128°C, $\mathbf{R_f}$: 0.39 (EtAc–*n*-hexane, 1:3). FTIR: 1741.56 (OAc), 1688.14 (NAc), and 1600.07 cm^{-1} (CN). ^1H NMR (600 MHz, $CDCl_3$): δ_H = 1.92, 1.94, 2.08, 2.30 (4s, each 3H, 4 OAc); 2.56 (s, 3H, NAc); 4.32 (dd, 2H, CH_2); 4.59 (dd, 1H, H-2′); 5.22 (m, 1H, H-3′); 5.61 (m, 1H, H-4′); 7.32, 7.43 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{6,5}$—H); 7.73 (d, 1H, J = 8.4 Hz, benzothiazole, C_4—H); 7.81 (d, 1H, J = 7.2 Hz, benzothiazole, C_7—H); 8.61 (d, 1H, HCN). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 20.52, 20.80, 22.09, 23.48 (4 OCO$\underline{C}H_3$); 35.40 (NCO$\underline{C}H_3$); 53.78 (C-4); 61.95 (CH_2); 63.73 (C-3); 71.02 (C-2); 120.43, 121.22, 123.70, 124.06, 126.34 (Ar—C); 132.71 (CH); 149.69, 151.39, 170.36, 185.24 (4 CO); 159.80 (NCO); 167.0 (CN, thiazol). *Anal*. Calcd for $C_{22}H_{25}N_3O_9S$ (507.51): C, 52.06; H, 4.97; N, 8.28%. Found: C, 51.56; H, 5.34; N, 8.40%.

***N*-(Benzothiazolyl-2-yl)-D-galactono-hydrazide (13)**

Method A. A solution of compound **1** (1.68 g, 10.16 mmol) in absolute EtOH–DMF (3:1) (30 mL) was added to a solution of gama-D-galactolactone (**12**) (1.81 g, 10.16 mmol) in EtOH (20 mL) and AcOH (2 mL). The reaction mixture was heated on a boiling water bath for 7 h. The precipitate that separated out after cooling was filtered, dried, and crystallized from EtOH–DMF to give colorless crystals (2.48 g, 71% yield); m.p. 188°C. FTIR: 3411.58 (OH), 3209.24 (N—H), and 1680.73 cm^{-1} (OCN). ^1H NMR (600 MHz, DMSO-d_6): δ_H = 3.41–3.45 (m, 3H, H-5′, 6′,6″); 3.49 (t, 1H, J = 9.6 Hz, H-4′); 3.74 (m, 1H, H-3′); 3.84 (t, 1H, J = 8.4 Hz, H-2′); 4.16, 4.25, 4.34, 4.35, 5.32 (5d, 5H, D_2O exchangeable, 5 OH); 7.07, 7.26 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{5,6}$—H); 7.41 (d, 1H, J = 7.8 Hz, benzothiazole, C_4—H); 7.71 (d, 1H, J = 7.2 Hz, benzothiazole, C_7—H); 9.78, 10.12 (2s, 2H, D_2O exchangeable, 2NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 56.07 (CH_2); 68.84 (C-2); 71.13 (C-3); 78.80 (C-4); 79.24 (C-5); 118.72, 121.27, 121.51, 125.71, 130.45, 152.35 (Ar—C); 170.57 (CN); 173.86 (OCN). *Anal*. Calcd for $C_{13}H_{17}N_3O_6S$ (343.36): C, 45.47; H, 4.99; N, 12.24%. Found: C, 45.56; H, 5.13; N, 12.29%.

Method B. A solution of compound **1** (1.68 g, 10.16 mmol) in absolute EtOH–DMF (3:1) (30 mL) was added to a solution of gama-D-galactolactone (**12**) (1.81 g, 10.16 mmol) in EtOH (20 mL) and AcOH (2 mL). The reaction mixture was sonicated at a frequency of 40 kHz for 5 min at 30°C and processed as before to give compound **13** (3.0 g, 86% yield); m.p. 178–180°C. IR and ^1H NMR spectra were superimposable with the spectra from method A.

***N^1*-Acetyl-*N^2*-(benzothiazolyl)-2-yl)-2,3,4,5,6-penta-*O*-acetyl-D-galacto-hydrazide (14).** A cold solution of compound **13** (0.54 g, 1.57 mmol) in dry pyridine (12 mL) was cooled in an ice bath, then treated with Ac_2O (20 mL) with stirring. The mixture was kept overnight at rt, then poured onto crushed ice. The product that separated out was filtered off, washed repeatedly with water, dried, and crystallized from EtOH to give colorless crystals (0.59 g, 64% yield); m.p. 138–140°C, $\mathbf{R_f}$: 0.23 (EtAc–*n*-hexane, 1:3). FTIR: 1740.28 (OAc) and 1712.33 cm^{-1} (NAc). ^1H NMR (600 MHz, $CDCl_3$): δ_H = 1.69 (s, 3H, NAc), 2.05, 2.11, 2.15, 2.19, 2.33 (5s, 15H, 5 OAc); 3.72 (q, 1H, H-5′); 3.97, 4.28 (2dd, 2H, H-6′,6″); 5.28 (t, 1H, H-3′); 5.57 (d, 1H, H-2′); 5.68 (dd, 1H, H-4′); 7.44, 7.98 (2t, each 1H, J = 7.2 Hz, benzothiazole, $C_{5,6}$—H); 7.87 (d, 1H, J = 7.8 Hz, benzothiazole, C_7—H); 7.95 (d, 1H, J = 8.4 Hz, benzothiazole, C_4—H); 8.96 (bs, 1H, D_2O exchangeable, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 20.36 (NCO$\underline{C}H_3$); 20.61, 20.65, 20.68, 21.0 (5 OCO$\underline{C}H_3$); 61.95 (CH_2); 68.29 (C-3); 67.58 (C-5); 68.60 (C-4); 67.33 (C-2); 121.01,121.29, 122.55, 124.70, 126.26, 133.79 (Ar—C); 169.82 (CN); 170.29 (N$\underline{C}OCH_3$); 170.45, 170.51, 170.54, (5 CO). *Anal*. Calcd for $C_{25}H_{29}N_3O_{12}S$ (595.58): C, 50.42; H, 4.91; N, 7.06%. Found: C, 50.91; H, 5.09; N, 7.52%.

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