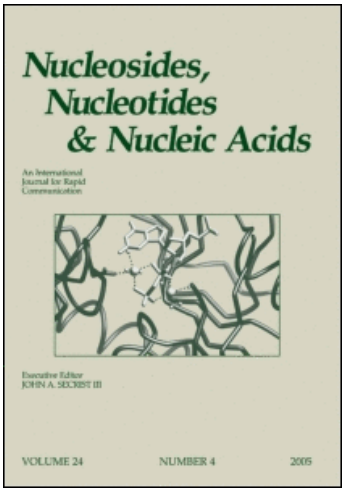

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Novel Regioselective Formation of S- and N-Hydroxyl-Alkyls of 5-(3-Chlorobenzo[*b*]Thien-2-yl)-3-Mercapto-4*H*-1,2,4-Triazole and A Facile Synthesis of Triazolo-Thiazoles and Thiazolo-Triazoles. Role of Catalyst and Microwave

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NOVEL REGIOSELECTIVE FORMATION OF S- AND N-HYDROXYL-ALKYLS OF 5-(3-CHLOROBENZO[*b*]THIEN-2-yl)-3-MERCAPTO-4*H*-1,2,4-TRIAZOLE AND A FACILE SYNTHESIS OF TRIAZOLO-THIAZOLES AND THIAZOLO-TRIAZOLES. ROLE OF CATALYST AND MICROWAVE

E. S. H. El Ashry, A. A. Kassem, H. Abdel-Hamid, F. F. Louis, Sh. A. N. Khattab, and M. R. Aouad □ *Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt*

□ *Regioselective alkylation of 5-(3-chlorobenzo[b]thien-2-yl)-4H-1,2,4-triazole (**1**) with hydroxy alkylating agents **2**, **3**, **13**, and the 2,3-O-isopropylidene-1-O-(p-tolylsulfonyl)-glycerol (**10**) afforded the corresponding S-alkylated derivatives **6**, **7**, **11**, and **14** under both conventional and microwave irradiation conditions; bentonite as a solid support gave better results, with no change in regioselectivity. A facile intramolecular dehydrative ring closure of **6**, **7**, **11**, and **14** using K_2CO_3 in DMF afforded the corresponding fused triazolo-thiazines and thiazolo-triazole **17–19**. The isopropylidenes and acetyl derivatives of the products were prepared.*

Keywords 1,2,4-Triazoles; regioselectivity; acyclonucleoside; thiazolo-triazole; triazolo-thiazines; microwave; solid support

INTRODUCTION

Compounds containing the benzo[*b*]thiophene are interesting class of fused heterocycles due to their versatile pharmacological properties[1–7] as antibiotic, analgesic, antioxidative, antiinflammatory, diuretic, enzyme inhibitor,[2] antiallergic,[3] and ocular hypotensive activities.[4] Moreover, they were useful for the treatment of osteoporosis in postmenopausal women[5,6] and estrogen dependant diseases.[7] Also, compounds with 1,2,4-triazole moiety possess important biological activities including antiinflammatory,[8] antitumorial,[9] antihypertensive,[10]

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anticonvulsant,[11] analgesic,[12] antagonist,[13] and fungicidal[14,15] activities. Some of these compounds were used as drugs such as fluotrimazol, ribavirine, furazonal, estazolam, alprazolam, rizatriptane, and fluconazole.[16–20]

Acyclonucleosides are a class of nucleosides in which the cyclic carbohydrate moiety was replaced by an acyclic side chain and were reviewed by El Ashry et al.[21] Alkylated heterocycles containing one or more hydroxyl groups on the alkyl side chain such as [9-(2-hydroxyethoxy)methyl]guanine (Acyclovir) and 9-(S)-(2,3-dihydroxypropyl)adenine (DHPA) exhibit antiviral and antitumor activities.[22–25] This promoted the modification of both of the acyclic glycone and aglycone of acyclonucleoside analogues.[26–32]

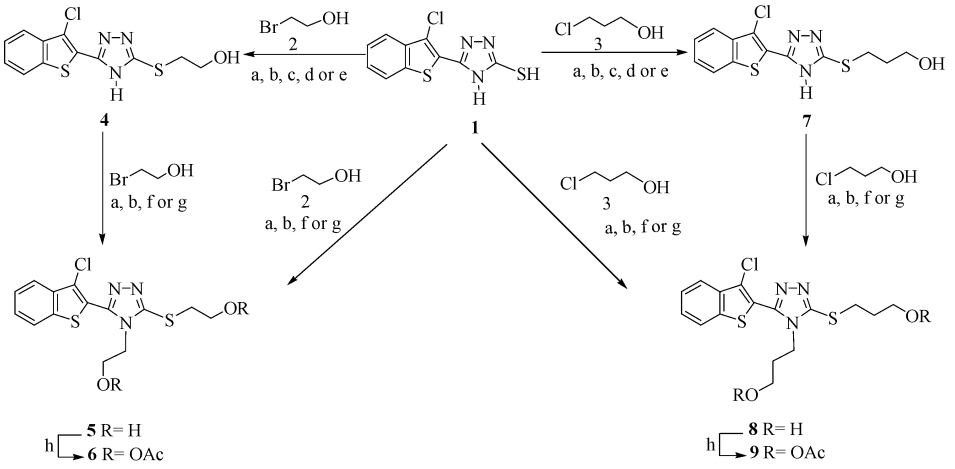
The utility of microwave (MW) as a nonconventional energy source has advantages as the significant rate-enhancements of reactions, higher product yields and greater selectivity of organic reactions.[34–36] The combination of solvent-free reaction conditions and microwave irradiation leads to simplicity in operation, less pollution and higher selectivity with several eco-friendly advantages in the context of green chemistry.[37–39]

Based on the above considerations and in continuation of our work on acyclonucleoside analogues,[40–42] we report herein the synthesis of new hydroxy-alkylation of the combined heterocycle 5-(3-chlorobenzo[*b*]thien-2-yl)-3-mercapto-4*H*-1,2,4-triazole and the intramolecular dehydrative ring closure of the S-hydroxyalkylated derivatives to triazolo-thiazoles and thiazolo-triazoles. The effect of solid support and MW in accelerating the synthesis have been investigated.

RESULTS AND DISCUSSION

In the present investigation, the S-(hydroxyl)alkylated analogues **4**, **7**, **11**, and **14** and S,N-bis(hydroxyl-alkylated) analogues **5**, **8**, **13**, and **15** were synthesized from 5-(3-chlorobenzo[*b*]thien-2-yl)-3-mercapto-4*H*-1,2,4-triazole (**1**). The strategy for synthesizing the target nucleoside analogues was based on the possible regioselective alkylation of **1** of one or two equivalents of the different hydroxy alkylating agents **2**, **3**, and **13** or the protected derivative 2,3-*O*-isopropylidene-1-*O*-(*p*-tolylsulfonyl)-glycerol (**10**) under both conventional and microwave methods (Scheme 1 and 2).

The reaction between **1** and 1.1 equivalent of **2**, **3**, **10**, and **13** in the presence of NaOEt or NaOAc as de-protonating agent in alcoholic solvent, required heating under reflux for 1.5–4.0 hours and 3–10 hours, respectively, to give only the S-alkylated analogues **4**, **7**, **11**, and **14** in 68–78%. De-protection of **11** with 70% acetic acid under conventional conditions, gave 5-(3-Chlorobenzo[*b*]thien-2-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-4*H*-1,2,4-triazole (**14**) whose reaction with acetone in presence of sulfuric acid gave back compound **11** (Scheme 1 and 2).

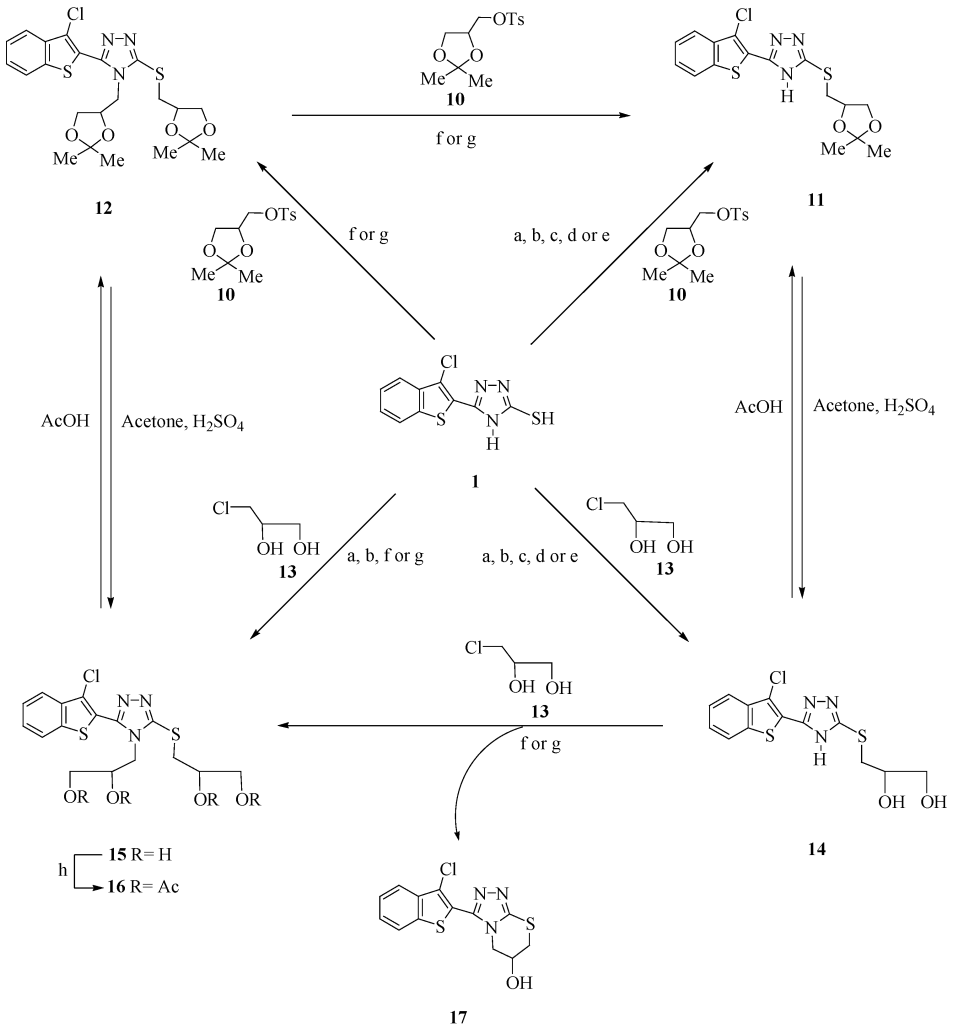


a) NaOEt, EtOH, reflux ; b) NaOEt, EtOH, MWI; c) NaOAc, MeOH, reflux, ; d) NaOAc, MeOH, MWI; e) Bentonite, MWI;f) K_2CO_3, DMF, reflux ; g) K_2CO_3, DMF, reflux, MWI;h) Ac_2O, Pyridine

SCHEME 1 Hydroxy-alkyl derivatives.

Much better yields were obtained when these reactions were carried out under MW for 1.5–4.0 minutes with no change in regioselectivity. The coupling under solvent free conditions has been also adopted under MW. Thus, a mixture of **1** with **2**, **3**, **10**, or **13** adsorbed on the solid surface of activated bentonite in a closed Teflon vessel was irradiated by MW for 1–3 minutes to afford 88–94% of compounds **4**, **7**, **11**, and **14**. The products were isolated by simple extraction from the solid mass followed by usual work up. The structures of products were assigned based on their spectral data as well as elemental analysis. The IR spectra of **4**, **7**, and **14** showed characteristic absorption band at 3386–3439 cm^{-1} due to the OH of the acyclic side chains.

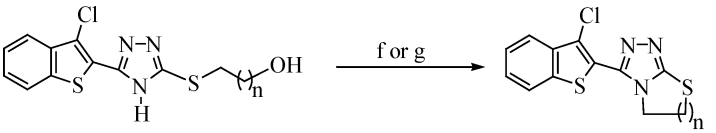
The ^1H NMR spectra of **4**, **7**, **11**, and **14** clearly indicated that a monoalkylation of **1** has taken place at the sulfur atom by showing one exchangeable proton at the downfield region at δ_H 11.92–14.50 ppm due to the NH-proton of the triazole ring. The OH protons of **4**, **7**, and **14** were assigned to the signal at δ_H 4.67–5.16 ppm. The spectrum of **14** showed a doublet of doublet at δ_H 3.19 and two multiplet at δ_H 3.35–3.43 and 3.70–3.75 ppm due to SCH_2, CH_2O, and CHO protons, respectively. The heteromultiple bond correlation ^1H-^1H DQFCOSY and ^1H-^{13}C NMR experiments facilitated the spectral assignment of **11** that showed two signals in the upper field region corresponding to the two methyls of the dioxalane ring. The SCH_2 protons appeared at δ_H 3.36, as a doublet of doublet of doublet, correlated with δ_c 35.2. The signals at δ_H 3.88 and 4.18 ppm as two doublet of doublets for CH_2O were correlated with their carbon at δ_c 68.5. The carbons assigned to CHO and $C(CH_3)_2$ appeared at δ_c 75.2 and 110.2, respectively.



a) NaOEt, EtOH, reflux; b) NaOEt, EtOH, MWI; c) NaOAc, MeOH, reflux ; d) NaOAc, MeOH, MWI; e) Bentonite, MWI; f) K_2CO_3, DMF, reflux ; g) K_2CO_3, DMF, MWI;h) Ac_2O, Pyridine

SCHEME 2 Glycerol derivatives.

Attempts to introduce the second acyclic side chain on the triazole ring using NaOAc as base under both conventional and microwave (MW) conditions were unsuccessful. The reaction of **1** with **2**, **3**, and **13** could proceed through the formation of S-nucleoside analogues **4**, **7**, **11**, and **14** as precursors for the formation of the bis(alkylated) analogues **5**, **8**, **13**, and **15**, presumably due to the higher nucleophilicity of the sulfur atom. Consequently, the sodium or potassium salts of the thiolate anions generated by proton-abstraction from the thiol groups under basic catalyst (NaOEt, NaOAc, and K_2CO_3) were initially formed and, hence, behaved as an ambident nucleophile in the nucleophilic substitution reactions. Further



4 n = 1
7 n = 2

18 n = 1
19 n = 2

f) K_2CO_3, DM, reflux ; g) K_2CO_3, DMF, MWI

SCHEME 3 Triazolo-thiazines and thiazolo-triazoles.

alkylation on the nitrogen of the triazole ring could be governed by the ability of these bases to abstract the hydrogen of the N-H group.

Direct coupling of the alkylating agents **2**, **3**, or **13** with **1** in boiling DMF in the presence of 1.1 equivalent of K_2CO_3 provided a mixture of the S-alkylated and S,N-bis(alkylated) derivatives in addition to some starting material. When these reactions were carried out with 2.2 equivalents of **2**, **3**, and **10** under reflux temperature in the presence of either K_2CO_3 or NaOEt for 6–20 hours, the corresponding S,N-bis(alkylated) analogues **5, 8**, and **12** were formed in 64–70% except in case of **12** which was not formed using NaOEt (Scheme 2). Alternatively, compound **15** was obtained via the isopropylidenation of **12**, which also was obtained by deprotection of compound **15** with 70% acetic acid. On the other hand, treatment of **1** with **13** using NaOEt as base afforded the S,N-bis(alkylated) derivative **15** in 62% yield. Surprisingly, when NaOEt was replaced by K_2CO_3 an unexpected product identified as triazolothiazine **17** was obtained in addition to compound **15** (Scheme 2). The formation of such cyclized product has presumably been a result of an intramolecular dehydrative cyclization reaction that followed the preliminary common S-alkylation; it could be a competitive reaction to the further alkylation on nitrogen- triazole atom. Similar cyclization of 6-amino-9-(3-hydroxypropyl)-7*H*-purine-8(9*H*)-thione to the anhydro analogue has been reported under Mitsunobu reaction condition.[43,44] The above simple conditions (K_2CO_3/DMF) for the intramolecular ring closure of hydroxyalkylated-S-heterocycles with N-4 of the ring have promoted us to develop a general synthetic procedure for the synthesis of triazolothiazines and thiazolotriazoles. Thus, the S-alkylated derivatives gave under the above conditions, the cyclized fused heterocycles **17–19** (Scheme 3) in moderate yields. Improvement of the isolated yields to 75–86% and significant reductions in reaction time has been achieved under the irradiation with MW (Table 1), thus, providing a simple route to the triazolo thiazines and thiazolotriazole.

The disappearance of NH-proton of the triazole ring in the IR and ^{1}H NMR spectra of **5**, **8**, **12**, **15**, **17**, **18**, and **19** confirmed its involvement in the reactions. The spectrum of **15** showed the appearance of four exchangeable protons, assigned to OH groups, instead of two for its precursor **14** which

TABLE 1 Comparative studies between conventional method (CM) and microwave (MW) method

	Conditions				Convventional method (CM)		Microwave method (MW)	
Compd. No.	Reagents*	Base	Solvent	Solid support	Time (hr)	Yield (%)	Time (min)	Yield (%)
4	a, b	NaOEt	EtOH	—	1.5	78	1.5	92
4	c, d	NaOAc	MeOH	—	3.0	77	2.0	89
4	e	—	—	Bentonite	—	—	1.0	94
5	a, b	NaOEt	EtOH	—	8.0	70	4.0	86
5	f, g	K_2CO_3	DMF	—	6.0	68	3.5	83
6	h	Pyridine	Ac_2O	—	24.0	80	—	—
7	a, b	NaOEt	EtOH	—	2.5	76	2.0	90
7	c, d	NaOAc	MeOH	—	7.0	73	2.5	88
7	e	—	—	Bentonite	—	—	1.0	93
8	a, b	NaOEt	EtOH	—	14.0	67	5.0	84
8	f, g	K_2CO_3	DMF	—	13.0	64	4.5	80
9	h	Pyridine	Ac_2O	—	24.0	75	—	—
11	a, b	NaOEt	EtOH	—	4.0	70	3.0	87
11	c, d	NaOAc	MeOH	—	9.0	69	4.0	83
11	e	—	—	Bentonite	—	—	3.0	88
12	f, g	K_2CO_3	DMF	—	20.0	66	5.0	79
14	a, b	NaOEt	EtOH	—	4.0	70	3.0	85
14	c, d	NaOAc	MeOH	—	10.0	68	4.0	82
14	e	—	—	Bentonite	—	—	2.5	90
15	a, b	NaOEt	EtOH	—	20.0	62	6.0	77
15, 17	f, g	K_2CO_3	DMF	—	18.0	60	5.0	75
16	h	Pyridine	Ac_2O	—	24.0	73	—	—
17	f, g	K_2CO_3	DMF	—	36.0	63	6.0	78
18	f, g	K_2CO_3	DMF	—	96.0	50	10.0	64
19	f, g	K_2CO_3	DMF	—	72.0	60	8.0	73

*See schemes.

confirmed the presence of two glycol side chains. On cyclization of **14** to **17**, the terminal OH disappeared and the terminal methylene protons was shifted to the down field region and assigned to the two doublets of doublets at δ_H 4.19 and 4.34 ppm. The assignment of both proton and carbon signals of compound **12** were based on the ^1H-^1H DQFCOSY experiments. Thus, the signals corresponding to the SCH_2 protons appeared as doublet of doublet of doublet at δ_H 3.52 ppm with J_{gem} 14.5 Hz whereas their coupling constants with the neighboring protons were 5.4 and 6.9 Hz. Both of the SCH_2 protons were correlated with the multiplet of the isopropylidene ring CHO at δ_H 4.48–4.55 ppm which in turn correlated with CH_2O(a) that resonated as two doublet of doublets at δ_H 3.85 and 4.16 ppm. Correlation of the carbon signals with those of the attached protons indicated that the SCH_2 carbon resonated at δ_C 36.9 whereas CHO and CH_2O were assigned at δ_C 74.7 and 68.5, respectively. On the other hand, the NCH_2 protons appeared as doublet of doublet and doublet of doublet of doublet at δ_H

4.23 and 4.29 ppm, which correlated with the multiplet of CHO(b), which in turn correlated with CH_2O(b) that resonated as multiplet and doublet of doublet at δ_H 4.00–4.04 and 4.16. Their respective carbons resonated at δ_C 51.3, 73.9, and 67.0, respectively.

Acetylation of **5**, **8**, and **15** with acetic anhydride in pyridine at room temperature afforded the protected acyclonucleoside analogues **6**, **9** and **16** in 73–80% yield. Their IR spectra showed the appearance of the carbonyl of the acetoxy group. Moreover, the appearance of singlet at higher field region at δ_H 2.06–2.13 ppm in the ^{1}H NMR spectra of compounds **6**, **9**, and **16** accompanied with the down field shift of the CH_2 attached to it confirming the assigned structures.

CONCLUSIONS

In conclusion, the alkylation of 5-(3-chlorobenzo[*b*]thien-2-yl)-4*H*-1,2,4-triazole-3-thiol (**1**) with the hydroxyalkylating agents **2**, **3**, **13**, and the protected derivative **10** in presence of NaOEt or NaOAc afforded selectively the hydroxyalkylated-S-heterocycles, which upon further alkylation using NaOEt or K_2CO_3 afforded the S,N-bis(alkylated) analogues **5**, **8**, **13**, and **15** under both conventional and microwave conditions. Moreover, much better results were obtained when bentonite was used as solid support. A facile route to the fused ring system triazolo-thiazine and thiazolo-triazole that linked to benzothiophene rings has been developed. Again the microwave technique in presence of bentonite is a good approach for the synthesis of the target acyclonucleoside analogues and fused heterocyles.

EXPERIMENTAL

General Methods

Melting points were determined with a Melt-Temp apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel (Merck) using ethyl acetate-hexane as developing solvents, and the spots were detected by UV light absorption. Irradiation was done in a domestic microwave oven EM-230M (1200 watt output power). IR spectra were recorded with Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded on Jeol spectrometer (500 MHz) and Bruker Avance spectrometer (300 MHz), while ^{13}C NMR spectra were recorded on Jeol spectrometer (125.7 MHz). The assignment of ^{1}H NMR spectra was based on chemical shift correlation DQFCOSY spectra, while the assignment of ^{13}C NMR spectra was based on HMQC experiments. Chemical shifts (δ) are given in ppm relative to the signal for TMS as internal standard. The elemental analyses were performed by the microanalysis unit at the Faculty of Science, Cairo University, Egypt.

General Procedure for the Alkylation of 5-(3-Chlorobenzo[*b*]thien-2-yl)-3-mercapto-4*H*-1,2,4-triazole (1)

Conventional Method (CM): To a solution of compound (1 mmol) in appropriate solvent (15 mL) and base (1.1 or 2.2 mmol), the appropriate hydroxyalkylating agents **2**, **3**, **13**, and 2,3-*O*-isopropylidene-1-*O*-(*p*-tolylsulfonyl)-glycerol (**10**) (1.1 or 2.2 mmol) were added with stirring. The reaction mixture was heated under reflux and then poured onto crushed ice. The obtained products were washed with water, dried, and recrystallized from ethanol or purified by column chromatography (Table 1).

Microwave Method (MW): A mixture of compound (1 mmol) in appropriate solvent (5 mL), base (1.1 or 2.2 mmol) and the appropriate alkylating agents **2**, **3**, **10**, and **13** (1.1 or 2.2 mmol) in a closed Teflon vessel were irradiated by MW. The obtained reaction mixture was treated as described above (Table 1).

MWI Method Using Solid Support: A mixture of **1** (1 mmol) and alkylating agent **2**, **3**, **10**, and **13** (1.1 mmol) were adsorbed on the solid surface of bentonite (0.3 g) in a closed Teflon vessel and then irradiated by MW. After cooling the products were extracted and crystallized by ethanol (Table 1).

5-(3-Chlorobenzo[*b*]thien-2-yl)-3-[(2-hydroxyeth-1-yl)thio]-4*H*-1,2,4-triazole (4). This compound was obtained as yellow needles, m.p.: 160–161°C, IR (KBr): 1500 (C=C), 1570 (C=N), 3221 (NH), 3386 (OH). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.30 (t, 2H, J = 6.4 Hz, SCH_2), 3.71 (t, 2H, J = 6.4 Hz, CH_2O), 5.13 (bs, 1H, D_2O exchangeable, OH), 7.50–8.09 (m, 4H, H-benzothiophene), 14.50 (s, 1H, D_2O exchangeable, NH). *Anal. Calcd.* for $C_{12}H_{10}ClN_3OS_2$ (311.81): C, 46.22; H, 3.23; N, 13.48. Found: C, 46.24; H, 3.48; N, 13.12.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(2-hydroxyeth-1-yl)-3-[(2-hydroxyeth-1-yl)-thio]-1,2,4-triazole (5). This compound was obtained as colorless crystals; m.p.: 142–143°C. IR (KBr): 1553 (C=C), 1567 (C=N), 3260–3389 (OH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.16 (bs, 1H, D_2O exchangeable, OH), 3.40 (dd, 2H, J = 4.6 Hz, J = 5.4 Hz, SCH_2), 4.06 (t, 2H, J = 4.6 Hz, CH_2O), 4.11 (t, 2H, J = 4.6 Hz, CH_2O), 4.27 (dd, 2H, J = 4.6 Hz, J = 5.4 Hz, NCH_2), 4.60 (s, 1H, D_2O exchangeable, OH), 7.41–7.47 (m, 2H, H-5, H-6 benzothiophene), 7.78 (d, 1H, J = 7.7 Hz, H-4 benzothiophene), 7.89 (d, 1H, J = 7.7 Hz, H-7 benzothiophene). *Anal. Calcd.* for $C_{14}H_{14}ClN_3O_2S_2$ (355.86): C, 47.25; H, 3.97; N, 11.81. Found: C, 47.38; H, 4.09; N, 11.98.

5-(3-Chlorobenzo[*b*]thien-2-yl)-3-[(3-hydroxyprop-1-yl)thio]-4*H*-1,2,4-triazole (7). This compoind was obtained as yellow needles; m.p.: 138–139°C, IR (KBr): 1525 (C=C), 1570 (C=N), 3190 (NH), 3439 (OH); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.79–1.82 (m, 2H, $CH_2CH_2CH_2$), 3.22 (t, 4H, J = 6.9 Hz, SCH_2, CH_2O), 4.67 (bs, 1H, D_2O exchangeable, OH), 7.47–7.53 (m, 2H, H-5, H-6 benzothiophene), 7.82 (d, 1H, J = 7.7

Hz, H-4 benzothiophene), 8.02 (d, 1H, $J = 6.9$ Hz, H-7 benzothiophene), 14.49 (s, 1H, D_2O exchangeable, NH). *Anal. Calcd.* for $C_{13}H_{12}ClN_3OS_2$ (325.84): C, 47.92; H, 3.71; N, 12.90. Found: C, 48.03; H, 3.80; N, 12.62.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(3-hydroxyprop-1-yl)-3-[(3-hydroxyprop-1-yl)-thio]-1,2,4-triazole (8). This compound was obtained colorless syrup after column chromatography (Eluant Hexane/EtOAc 6/4); IR (KBr): 1551 (C=C), 1575 (C=N), 3240–3360 (OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.97–2.01 (m, 2H, $SCH_2CH_2CH_2$), 2.07–2.12 (m, 2H, $NCH_2CH_2CH_2$), 2.70 (bs, 1H, D_2O exchangeable, OH), 3.50 (t, 2H, $J = 6.1$ Hz, SCH_2), 3.71 (t, 2H, $J = 6.1$ Hz, NCH_2), 3.76 (t, 2H, $J = 6.1$ Hz, CH_2O), 4.27 (t, 2H, $J = 6.1$ Hz, CH_2O), 4.66 (bs, 1H, D_2O exchangeable, OH), 7.39–7.46 (m, 2H, H-5, H-6 benzothiophene), 7.78 (d, 1H, $J = 7.7$ Hz, H-4 benzothiophene), 7.88 (d, 1H, $J = 7.7$ Hz, H-7 benzothiophene). *Anal. Calcd.* for $C_{16}H_{18}ClN_3O_2S_2$ (383.92): C, 50.06; H, 4.73; N, 10.95. Found: C, 50.34; H, 4.87; N, 11.14.

General procedure for the isoprpylidenation. Compound **14** or **15** (0.25 mmol) was stirred vigorously with dry acetone (10 mL) and 96% H_2SO_4 (3 drops) for 2 hours, and then kept for overnight at room temperature. The resulting mixture was neutralized by Na_2CO_3, filtered, and the inorganic salts were well washed with dry acetone. The filtrate was evaporated under reduced pressure and the resulting product that separated out was filtered off and crystallized from ethanol or purified by column chromatography.

5-(3-Chlorobenzo[*b*]thien-2-yl)-3-[(2,3-*O*-isopropylidene-2,3-dihydroxyprop-yl)thio]-4*H*-1,2,4-triazole (11). This compound was obtained as colorless crystals in (73% yield from **14**); m.p.: 146–148°C, IR (KBr): 1552 (C=C), 1581 (C=N), 3212 (NH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40, 1.49 (2 s, 6H, 2 × CH_3), 3.36 (ddd, 2H, $J = 5.4$ Hz, $J = 8.4$ Hz, $J = 14.5$ Hz, SCH_2), 3.88 (dd, 1H, $J = 6.9$ Hz, $J = 8.4$ Hz, CH_2O), 4.18 (dd, 1H, $J = 6.1$ Hz, $J = 8.4$ Hz, CH_2O), 4.49–4.54 (m, 1H, CHO), 7.45–7.50 (m, 2H, H-5, H-6 benzothiophene), 7.84 (d, 1H, $J = 6.9$ Hz, H-4 benzothiophene), 7.89 (d, 1H, $J = 6.9$ Hz, H-7 benzothiophene), 11.92 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 25.7, 27.0 (2 × CH_3), 35.2 (SCH_2), 68.5 (CH_2O), 75.2 (CHO), 110.2 ($C(CH_3)_2$), 122.6, 122.8, 125.5, 126.9, 137.0 (Ar-C). Anal. Calcd. for $C_{16}H_{16}ClN_3O_2S_2$ (381.90): C, 50.32; H, 4.22; N, 11.00%. Found: C, 50.60; H, 4.31; N, 10.95%.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(2,3-*O*-isopropylidene-2,3-dihydroxyprop-1-yl)-3-[(2,3-*O*-isopropylidene-2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (12). This compound was obtained as colorless syrup (69% yield from **15**) after column chromatography (Eluant Hexane/ EtOAc 25/1); IR (KBr): 1553 (C=C), 1571 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33, 1.35, 1.41, 1.45 (4 s, 12H, 4 × CH_3), 3.52 (ddd, 2H, $J = 5.4$ Hz, $J = 6.9$ Hz, $J =$ 14.5 Hz, SCH_2), 3.85 (dd, 1H, $J = 6.1$ Hz, $J = 8.4$ Hz, CH_2O(a)), 4.00–4.04 (m, 1H, CH_2O(b)), 4.16 (dd, 2H, $J = 6.1$ Hz, $J = 8.4$ Hz, CH_2O(a),

CH_2O(b)), 4.23 (dd, 1H, J = 5.4 Hz, J = 14.5 Hz, NCH_2), 4.28 (ddd, 1H, J = 3.1 Hz, J = 6.1 Hz, J = 14.5 Hz, NCH_2), 4.48–4.55 (m, 2H, 2 × CHO), 7.39–7.46 (m, 2H, H-5, H-6 benzothiophene), 7.79 (d, 1H, J = 7.7 Hz, H-4 benzothiophene), 7.88 (d, 1H, J = 8.4 Hz, H-7 benzothiophene). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 25.3, 25.5, 26.8, 27.1 (4 × CH_3), 36.9 (SCH_2), 51.3 (NCH_2), 67.0 (CH_2O(b)), 68.5 (CH_2O(a)), 73.9 (CHO(b)), 74.7 (CHO(b)), 109.9, 110.2 (2 × $C(CH_3)_2$), 122.5, 122.6, 125.1, 126.3, 137.2 (Ar-C). *Anal. Calcd.* for $C_{22}H_{26}ClN_3O_4S_2$ (496.04): C, 53.27; H, 5.28; N, 8.47. Found: C, 53.49; H, 5.46; N, 8.41.

General procedure for the deisopropylidenation. The isopropylidene **11** or **12** (5 mmol) was dissolved in 70% AcOH (5 mL). The mixture was heated under reflux for 2 hours. The solvent was evaporated under reduced pressure and the resulting product was collected and crystallized from ethanol (Table 1).

5-(3-Chlorobenzo[*b*]thien-2-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-4*H*-1,2,4-triazole (14). This compound was as yellow crystals (67% yield from **11**); m.p.: 112–114°C; IR (KBr): 1515 (C=C), 1578 (C=N), 3397 (br NH, OH); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.19 (dd, 1H, J = 7.7 Hz, J = 13.0 Hz, SCH_2), 3.35–3.43 (m, 3H, SCH_2, CH_2O), 3.70–3.75 (m, 1H, CHO), 4.77 (bs, 1H, D_2O exchangeable, OH), 5.16 (bs, 1H, D_2O exchangeable, OH), 7.49–7.59 (m, 2H, H-5, H-6 benzothiophene), 7.84 (d, 1H, J = 6.9 Hz, H-4 benzothiophene), 8.05 (d, 1H, J = 6.9 Hz, H-7 benzothiophene), 14.45 (s, 1H, D_2O exchangeable, NH). *Anal. Calcd.* for $C_{13}H_{12}ClN_3O_2S_2$ (341.84): C, 45.68; H, 3.54; N, 12.29. Found: C, 45.90; H, 3.38; N, 12.02.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(2,3-dihydroxyprop-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (15). This compound was obtained as colorless crystals (65% yield from **12**); m.p.: 128–129°C; IR (KBr): 1552 (C=C), 1572 (C=N), 3205–3355 (OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.21 (2dd, 1H, J = 5.4 Hz, J = 13.0 Hz, SCH_2), 3.33–3.45 (m, 5H, SCH_2, 2 × CH_2O), 3.71–3.77 (m, 1H, CHO), 3.86–3.92 (m, 1H, CHOH), 4.06 (dd, 1H, J = 8.4 Hz, J = 14.5 Hz, NCH_2), 4.25 (dd, 1H, J = 3.8 Hz, J = 14.5 Hz, NCH_2), 4.72 (bs, 1H, D_2O exchangeable, OH), 4.82 (bs, 1H, D_2O exchangeable, OH), 5.12 (bs, 2H, D_2O exchangeable, OH), 7.48–7.54 (m, 2H, H-5, H-6 benzothiophene), 7.83 (d, 1H, J = 6.9 Hz, H-4 benzothiophene), 8.04 (d, 1H, J = 6.9 Hz, H-7 benzothiophene). *Anal. Calcd.* for $C_{16}H_{18}ClN_3O_4S_2$ (415.92): C, 46.20; H, 4.36; N, 10.10. Found: C, 46.36; H, 4.75; N, 9.94.

General procedure for acetylation. To a cold solution of **5**, **8**, or **15** (1 mmol) in dry pyridine (5 mL) was added acetic anhydride (7 mL), the reaction mixture was kept for overnight at room temperature, poured onto ice-cold water. The crude product was filtered off and crystallized from ethanol or purified by column chromatography.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(2-acetoxyeth-1-yl)-3-[(2-acetoxyeth-1-yl)thio]-1,2,4-triazole (6). This compound was obtained as colorless plates; m.p.: 100–101°C; IR (KBr): 1552 (C=C), 1568 (C=N), 1741 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.07, 2.09 (2s, 6H, 2 × OAc), 3.58 (t, 2H, J = 6.2 Hz, SCH_2), 4.41–4.53 (m, 6H, NCH_2, 2 × CH_2 OAc), 7.44–7.49 (m, 2H, H-5, H-6 benzothiophene), 7.81–7.84 (m, 1H, H-4 benzothiophene), 7.90–7.93 (m, 1H, H-7 benzothiophene). *Anal. Calcd.* for $C_{18}H_{18}ClN_3O_4S_2$ (439.94): C, 49.14; H, 4.12; N, 9.55. Found: C, 49.53; H, 3.89; N, 9.23.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(3-acetoxyprop-1-yl)-3-[(3-acetoxyprop-1-yl)thio]-1,2,4-triazole (9). This compou d was obtained as colorless syrup after column chromatography (Eluant Hexane/EtOAc 4/1); IR (KBr) ν_{max} 1558 (C=C), 1580 (C=N), 1735 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.07, 2.08 (2 s, 6H, 2 × OAc), 2.16–2.21 (m, 2H, CH_2CH_2 OAc), 2.23–2.28 (m, 2H, CH_2CH_2 OAc), 3.39 (t, 2H, J = 6.9 Hz, SCH_2), 4.13 (t, 2H, J = 6.1 Hz, NCH_2), 4.23 (t, 4H, 2 × CH_2 OAc), 7.41–7.48 (m, 2H, H-5, H-6 benzothiophene), 7.81 (d, 1H, J = 7.7 Hz, H-4 benzothiophene), 7.93 (d, 1H, J = 7.7 Hz, H-7 benzothiophene). *Anal. Calcd.* for $C_{20}H_{22}ClN_3O_4S_2$ (467.99): C, 51.33; H, 4.74; N, 8.98. Found: C, 51.55; H, 4.60; N, 9.16.

5-(3-Chlorobenzo[*b*]thien-2-yl)-4-(2,3-di-acetoxyprop-1-yl)-3-[(2,3-diacetoxy-prop-1-yl)thio]-1,2,4-triazole (16). This compound was obtained as colorless syrup after column chromatography (Eluant Hexane/EtOAc (3:1)); IR (KBr): 1553 (C=C), 1571 (C=N), 1746 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.06, 2.09, 2.13 (3 s, 12H, 4 × OAc), 3.59 (ddd, 1H, J = 2.6 Hz, J = 6.9 Hz, J = 14.2 Hz, SCH_2), 3.79 (dd, 1H, J = 4.9 Hz, J = 14.2 Hz, SCH_2), 4.17–4.29 (m, 2H, NCH_2), 4.38–4.47 (m, 4H, 2 × CH_2 OAc), 5.42–5.47 (m, 2H, 2 × CHOAc), 7.43–7.48 (m, 2H, H-5, H-6 benzothiophene), 7.83 (dd, 1H, J = 2.0 Hz, J = 6.3 Hz, H-4 benzothiophene), 7.92 (dd, 1H, J = 2.0 Hz, J = 7.2 Hz, H-7 benzothiophene). *Anal. Calcd.* for $C_{24}H_{26}ClN_3O_8S_2$ (584.06): C, 49.35; H, 4.49; N, 7.19. Found: C, 49.65; H, 4.42; N, 7.23.

General Procedure for Intramolecular Cyclization

Conventional method (CM). To a solution of **4**, **7**, or **14** (1 mmol) and potassium carbonate (1.5 mmol) in DMF (15 mL) was heated under reflux. The reaction mixture was then poured onto crushed ice (10 mL). The product was filtered out and recrystallized from ethanol (Table 1).

Microwave method (MW). A mixture of 4, 7, or 14 (1 mmol) and potassium carbonate (1.5 mmol) in DMF (5 mL) in a closed Teflon vessel was irradiated. The obtained reaction mixture was treated as described above (Table 1).

3-(3-Chlorobenzo[*b*]thien-2-yl)-6-hydroxy-5*H*,7*H*-1,2,4-triazolo[3,4-*b*][1,3]thiazine (17). This compound was obtained as colorless crystals; m.p.: 210–212°C; IR (KBr): 1552 (C=C), 1572 (C=N), 3205 (OH). ^{1}H NMR

(500 MHz, DMSO-d_6) δ: 3.23 (dd, 1H, J = 6.7 Hz, J = 13.4 Hz, SCH_2), 3.45 (dd, 1H, J = 2.9 Hz, J = 13.4 Hz, SCH_2), 4.19 (dd, 1H, J = 3.9 Hz, J = 13.4 Hz, NCH_2), 4.34 (dd, 1H, J = 2.9 Hz, J = 13.4 Hz, NCH_2), 4.48–4.53 (m, 1H, CHO), 5.81 (d, 1H, J = 13.4 Hz, D_2O exchangeable, OH), 7.48–7.54 (m, 2H, H-5, H-6 benzothiophene), 7.83 (d, 1H, J = 6.9 Hz, H-4 benzothiophene), 8.04 (d, 1H, J = 6.9 Hz, H-7 benzothiophene). *Anal. Calcd.* for $C_{13}H_{10}ClN_3OS_2$ (323.82): C, 48.22; H, 3.11; N, 12.98. Found: C, 48.37; H, 3.22; N, 13.14.

3-(3-Chlorobenzo[*b*]thien-2-yl)-5*H*,6*H*-[1,3]thiazolo[2,3-*c*]-1,2,4-triazole (18). This compound was obtained as colorless crystals; m.p.: 125–126°C; IR (KBr): 1560 (C=C), 1578 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.28 (dd, 2H, J = 6.1 Hz, J = 13.0 Hz, SCH_2), 3.69 (dd, 2H, J = 6.1 Hz, J = 13.0 Hz, NCH_2), 7.45–7.52 (m, 2H, H-5, H-6 benzothiophene), 7.85 (dd, 1H, J = 2.3 Hz, J = 6.1 Hz, H-4 benzothiophene), 7.90 (dd, 1H, J = 2.3 Hz, J = 6.1 Hz, H-7 benzothiophene). *Anal. Calcd.* for for $C_{12}H_8ClN_3S_2$ (293.80): C, 49.06; H, 2.74; N, 14.30. Found C, 49.22; H, 2.90; N, 14.38.

3-(3-Chlorobenzo[*b*]thien-2-yl)-5*H*,6*H*,7*H*-1,2,4-triazolo[3,4-*b*][1,3]thiazine (19). This compound was obtainned as yellow plates; m.p.: 137–138°C; IR (KBr): 1570 (C=C), 1594 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.80–1.89 (m, 2H, $CH_2CH_2CH_2$), 3.25 (t, 2H, J = 7.1 Hz, SCH_2), 3.52 (t, 2H, J = 6.1 Hz, NCH_2), 7.51–7.58 (m, 2H, H-5, H-6 benzothiophene), 7.85–7.88 (m, 1H, H-4 benzothiophene), 8.05–8.09 (m, 1H, H-7 benzothiophene). *Anal. Calcd.* for $C_{13}H_{10}ClN_3S_2$ (307.82): Calcd C, 50.72; H, 3.27; N, 13.65. Found C, 50.93; H, 3.40; N, 13.49.

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