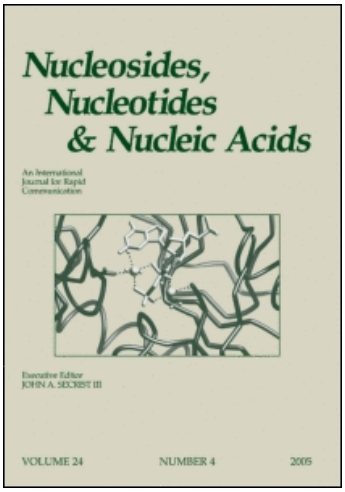

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Novel Regioselective Hydroxyl-Alkylation of 4,5-Diphenylimidazole-2-Thione and A Competitive Intramolecular Ring Closure of the S-Hydroxyalkyl-Imidazoles to Imidazo[2,1-*b*]Thiazines and Thiazoles. Role of Catalyst, Microwave Irradiation, and Solid Support

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NOVEL REGIOSELECTIVE HYDROXYL-ALKYLATION OF 4,5-DIPHENYLIMIDAZOLE-2-THIONE AND A COMPETITIVE INTRAMOLECULAR RING CLOSURE OF THE S-HYDROXYALKYL-IMIDAZOLES TO IMIDAZO[2,1-*b*]THIAZINES AND THIAZOLES. ROLE OF CATALYST, MICROWAVE IRRADIATION, AND SOLID SUPPORT

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□ *Under both conventional method (CM) and microwave (MW) irradiation (MWI) conditions, alkylation of 4,5-diphenylimidazole-2-thione (**1**) with halogeno-alkanols **2** or **5**, chloroglycerol **11** and 2,3-O-isopropylidene-1-O-(p-tolylsulfonyl)-glycerol (**8**) in presence of sodium ethoxide or sodium acetate in alcohol afforded regioselectively the corresponding S-alkylated analogues **3**, **6**, **9**, and **12**; they also were obtained using MW in absence and presence of bentonite as solid support with no change in regioselectivity. In the presence of potassium carbonate in DMF, the bisalkylated analogues **4**, **7**, **10**, and **13** were obtained except in case of compound **13** where it was accompanied with the imidazothiazine **14**. A convenient approach for imidazo-[2,1-b]thiazines and thiazoles **14–16** could be achieved by intramolecular dehydrative ring closure of the S-hydroxyalkylated imidazoles **3**, **6**, and **12** using potassium carbonate in DMF under both conventional and microwave methods. Isopropylidenation of **12** and **13** and deprotection of **9** and **10** also were investigated.*

Keywords Imidazole; imidazo[2,1-*b*][1,3]thiazine; Imidazo[2,1-*b*][1,3]thiazole; acyclonucleoside; alkylation; microwave irradiation; solid support

INTRODUCTION

Many acyclonucleoside analogues[1] such as acyclovir[2] (ACV), ganciclovir[3] (GCV) and penciclovir[4] (PCV), and (*S*)-9-(2,3-dihydroxypropyl)adenine[5] posses potent antiviral activity. Extensive efforts have

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been directed to synthesize acyclonucleoside analogues of the natural ones by modification of the heterocyclic base and/or the acyclic side chain.[1,6–11]

Valuable medicinal applications such as antiinflammatory,[12] antiasthmatic,[13] antiulcerative[14] and antithrombotic[15] activities have been associated with 2-thiosubstituted imidazoles and diaryl imidazoles.

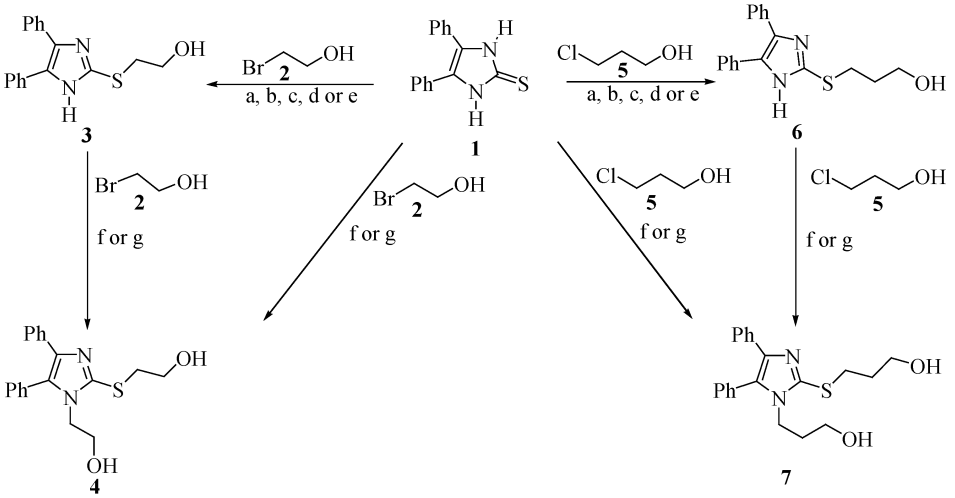
Microwave technology has opened up new horizons for chemists and increasingly used to accelerate organic reactions.[16–20] The solvent free conditions also have been adopted to organic synthesis as a tool for green chemistry[21–24] particularly when coupled to microwave irradiation.

On the basis of these findings, it was of interest to report on the regioselectivity encountered and the intramolecular anellation to form imidazothiazine and imidazothiazole during the synthesis of acyclonucleoside analogues from the 4,5-diphenylimidazole-2-thione[25] under both conventional method (CM) and microwave (MW) as a continuation of a program directed to use microwave technology in our laboratory.[16,17,26–36] The competitive intramolecular cyclization with the N-hydroxylalkylation can be explained by the semiemperical AM1 theoritical calculations.

RESULTS AND DISCUSSION

This work describes the regioselective alkylation of 4,5-diphenylimidazole-2-thione (**1**) by reaction with one and two equivalents of different hydroxyl-alkylating agents including halogeno-ethanol **2**, propanol **5**, 2,3-dihydroxychloropropanol **11** and 2,3-*O*-isopropylidene-1-*O*-(*p*-tolylsulfonyl)-glycerol (**8**) under both conventional and microwave methods. Reaction of **1** with 1.1 equivalents of **2**, **3**, **8**, and **11** in a boiling solution of sodium ethoxide in ethanol for 2–6 hours or in boiling methanol in the presence of NaOAc for 4-14 hours afforded only the S-alkyl derivatives **3**, **6**, **9**, and **12**, respectively in 62–74%. Deprotection of **9** with 70% acetic acid at reflux temperature gave the corresponding 2-(2,3-dihydroxyprop-1-ylthio)-4,5-diphenylimidazole (**12**) whose reaction with acetone in sulfuric acid gave back compound **9** (Schemes 1 and 2). When the above reactions were carried out under MW, 1–5 minutes were required to give the same products in higher yields (Table 1), and no change in regioselectivity was noticed. A higher yield (79–88%) was achieved under MW irradiation for 1–3 minutes of a mixture of **1** with the alkylating agent adsorbed on the surface of the bentonite in a closed Teflon vessel.

The structures of the S-alkylated compounds have been established on the basis of their elemental analyses and spectral data. The IR spectra of **3**, **6**, and **12** showed characteristic absorption band at 3314—3413 cm^{-1} due to OH of the acyclic side chains. Their ^1H NMR spectra indicated the



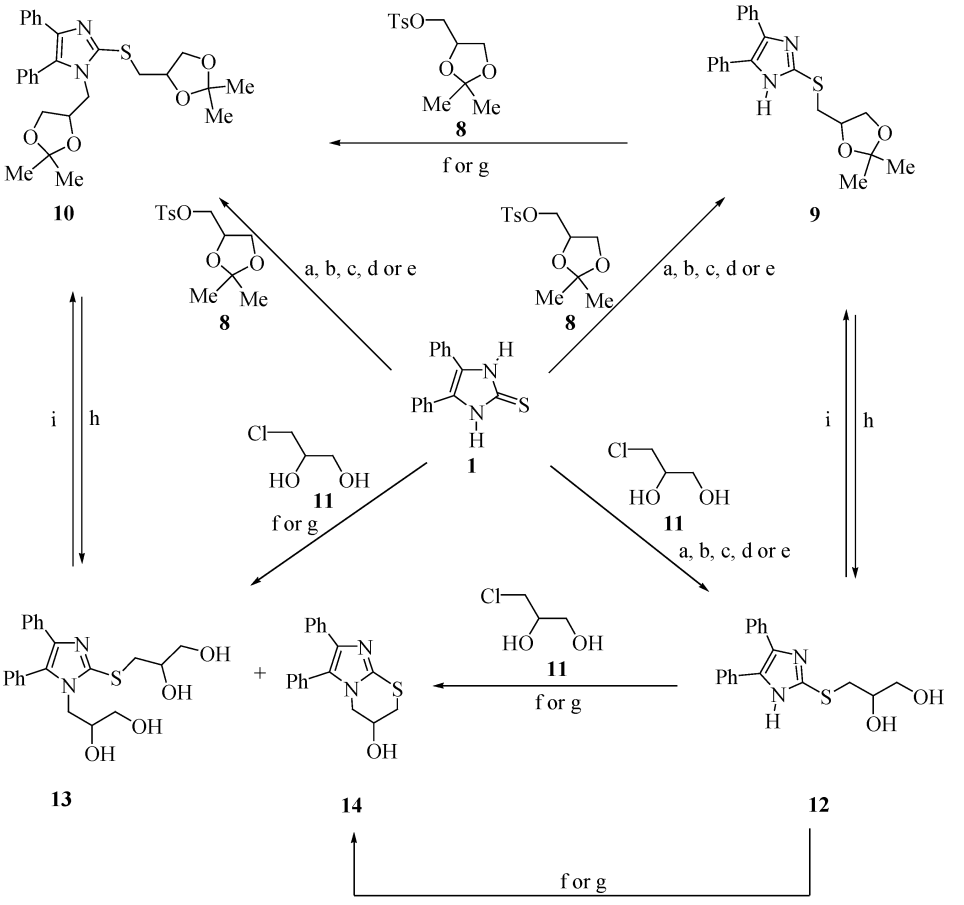
a) NaOEt, EtOH, reflux, CM; b) NaOEt, EtOH, MW;
c) NaOAc, MeOH, reflux, CM; d) NaOAc, MeOH, MW;
e) Bentonite, MW;
f) K_2CO_3, DMF, reflux, CM; g) K_2CO_3, DMF, MW

SCHEME 1 Reaction of imidazole thione with halogeno-ethanol and propanol.

TABLE 1 Comparative results from conventional method (CM) and microwave (MW) method

	Conditions					Conventional method (CM)		Microwave method (MW)	
Compd. No.	Alkylating agent	Entry*	Base	Solvent	Solid support	Time (hr)	Yield (%)	Time (min)	Yield (%)
3	**2**	a, b	NaOEt	EtOH	—	2.0	74	1.0	89
3	**2**	c, d	NaOAc	MeOH	—	4.0	70	2.0	84
3	**2**	e	—	—	Bentonite	—	—	1.0	88
4	**2**	f, g	K_2CO_3	DMF	—	8.0	66	4.0	81
6	**3**	a, b	NaOEt	EtOH	—	3.0	72	2.0	88
6	**3**	c, d	NaOAc	MeOH	—	6.0	69	2.5	82
6	**3**	e	—	—	Bentonite	—	—	1.5	86
7	**3**	f, g	K_2CO_3	DMF	—	10.0	65	4.5	76
9	**5**	a, b	NaOEt	EtOH	—	06.0	67	3.0	82
9	**5**	c, d	NaOAc	MeOH	—	14.0	62	5.0	76
9	**5**	e	—	—	Bentonite	—	—	3.0	79
10	**5**	f, g	K_2CO_3	DMF	—	20.0	62	5.0	75
12	**4**	a, b	NaOEt	EtOH	—	05.0	69	3.0	81
12	**4**	c, d	NaOAc	MeOH	—	10.0	65	4.0	76
12	**4**	e	—	—	Bentonite	—	—	3.0	79
13, 14	**4**	f, g	K_2CO_3	DMF	—	14.0	68	6.0	79
14	—	f, g	K_2CO_3	DMF	—	48.0	60	4.0	70
15	—	f, g	K_2CO_3	DMF	—	96.0	65	6.0	78
16	—	f, g	K_2CO_3	DMF	—	72.0	55	4.0	65

*See Scheme.



a) NaOEt, EtOH, boil, CM; b) NaOEt, EtOH, MW;
c) NaOAc, MeOH, boil, CM;d) NaOAc, MeOH,MW;
e) Bentonite, MW; f) K_2CO_3, DMF, boil, CM;
g) K_2CO_3, DMF, MW; h) AcOH, H_2O; i) Acetone, H_2SO_4

SCHEME 2 Reaction of imidazolethione with glycerol derivatives.

formation of the S-alkylated products by the assignment of one exchangeable proton at δ_H 12.54–12.61 due to a one NH proton of the imidazole ring. Moreover, the OH protons of **3** and **6** were assigned to the singlets at δ_H 5.13 and 4.72, respectively. The spectrum of **12** showed two doublet of doublets of the SCH_2 at δ_H 3.14 and 3.31 ppm, which were correlated with the multiplet at δ_H 3.7–3.7 ppm of C*H*O whereas their respective carbons were assigned at δ_c 37.2 and 71.8, respectively. The multiplet at δ_H 3.35–3.43 ppm for CH_2O was correlated with its corresponding carbon at δ_c 64.5. The spectrum of **12** also showed a triplet at δ_H 4.98 and a singlet at δ_H 5.45, which were assigned to the OH groups.

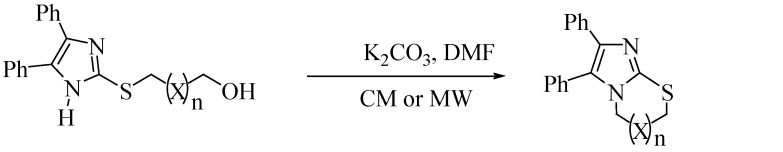
The ^{1}H NMR spectrum of compound **9** has two doublet of doublets at δ_H 3.20 and 3.27 ppm corresponding to the SCH_2 protons, whereas the two doublet of doublets at δ_H 3.80 and 4.16 were assigned to the CH_2O protons. Its ^{13}C NMR spectrum showed signals at δ_c 36.8, 68.4, 77.1, and 110.1 corresponding to S*C*H_2, *C*HO, -*C*H_2O, and Me_2C, respectively.

Attempted preparation of the acyclonucleosides **4**, **7**, **10**, and **13** from **1** by using 2.2 equivalents of the alkylating agents **2**, **5**, and **8** in presence of NaOEt or NaOAc in alcoholic solvent was unsuccessful. On the other hand, in the presence of K_2CO_3 in boiling DMF as base for 8–20 hours the corresponding acyclonucleosides analogues **4**, **7**, and **12** were successfully obtained in 62–66% yield. The use of 1.1 equivalent of the alkylating agent in presence of K_2CO_3 in boiling DMF gave a mixture of the S-alkylated and S,N-bis(alkylated) derivatives as well as some starting material. Isopropylidenation of **13** gave **10** whose deprotection gave **13**.

Unexpectedly, reaction of **1** with **11** under the same condition did not only afford the S,N-bis(dihydroxypropyl) **13**, but an additional product was obtained and identified as imidazothiazine **14** (Scheme 2). The identity of such cyclized product indicated that its precursor would be the respective monoalkylated derivative **12**. The formation of the two products has reflected that a competitive reaction, following the preliminary common S-alkylation, between the intramolecular dehydrative cyclization reaction and the further alkylation on the nitrogen-imidazole atom has taken place. Such tendency of intramolecular ring closure has prompted us to apply these conditions, K_2CO_3 in DMF, to the S-alkylated analogue **12** whereby the cyclized product was formed as a sole product. Moreover, the cyclization of **3** or **6** gave **15** and **16**, respectively, under similar conditions, indicating the generality of these conditions to achieve such intramolecular cyclization and it is favorable that the S-alkylated derivatives were the intermediates. Although, the cyclizations required heating for long periods of times, much shorter times were only needed under the MW to give even better yields (Table 1). Mitsunobu reaction condition[37,38] was used to achieve the cyclization of 6-amino-9-(3-hydroxypropyl)-7*H*-purine-8(9*H*)-thione to the anhydro analogue.

The structures of the fused heterocyles were deduced from the analysis of their spectra. The IR and the ^{1}H NMR spectra showed the disappearance of NH proton of the imidazole ring. The ^{1}H NMR spectrum of **14** indicated that the terminal OH of its precursor **12** disappeared upon the cyclization and the multiplet of the terminal methylene protons of **12** was shifted to the downfield region as two doublets of doublets at δ_H 3.55 and 3.76 ppm.

In order to explain the observed difference in the mode of reaction of **1** with the different alkylating agents and the competitive intramolecular cyclization with the formation of acyclonucleoside analogues, the semiemperical AM1 theoretical methods, carried out with MOPAC7 program pack-



12 X = CHOH, n = 1
3 X = n = 0
6 X = CH_2, n = 1

14 X = CHOH, n = 1
15 X = n = 0
16 X = CH_2, n = 1

EQUATION 1 Synthesis of imadazo-thiazones and thaizoles.

age has been used. Thus, the heat of formation for the mono S-alkylated derivatives **3, 4**, and **12** and the S,N-bis(alkylated) products **4, 7**, and **13** as well as the respective fused rings **14–16** have been calculated. The higher stability of the S-alkylated product **12** ($\Delta H = -2.95$ Kcal·mol^{-1}) compared to other analogues **3** and **6** ($\Delta H = 48.06$ and 41.38 Kcal·mol^{-1}, respectively) allowed a more chance of intramolecular dehydrative cyclization to take place to give **14** in addition to the alkylation to give **13**. Moreover, the lower heat of formation of imidazo-thiazine **14** ($\Delta H = 59.69$ Kcal·mol^{-1}) than that of the other fused imidazo derivative **15** and **16** ($\Delta H = 119.15$ and 106.26 Kcal·mol^{-1}, respectively) facilitated its formation (Table 2). The imidazo-thiazines **14** and **16** were found to be more stable than the imidazo-thiazole which is reflected in the higher yields of **14** and **16** compared to **15** which was accompanied with a recovered starting material.

The energy difference (ΔE_1 −71.09 and ΔE_3 −64.88 Kcal·mol^{-1}) between the mono-S-alkylated products **3** and **6** and their corresponding fused rings were higher than that between the mono alkylated derivatives and the bis-alkylated analogues ($\Delta E_2 = 46.67$ and $\Delta E_4 = 51.54$ Kcal·mol^{-1},

TABLE 2 Heat of formation of products

Compd. No.	Heat of formation ΔH (Kcal. mol^{-1})	Energy difference ΔE (Kcal. mol^{-1})
3	48.06	
4	1.39	$\Delta E_1 = \Delta H(\mathbf{3}) - \Delta H(\mathbf{4}) = 46.67$
15	119.15	$\Delta E_2 = \Delta H(\mathbf{3}) - \Delta H(\mathbf{15}) = -71.09$
6	41.38	
7	−10.16	$\Delta E_3 = \Delta H(\mathbf{6}) - \Delta H(\mathbf{7}) = 51.54$
16	106.26	$\Delta E_4 = \Delta H(\mathbf{6}) - \Delta H(\mathbf{16}) = -64.88$
12	−2.95	
13	−98.02	$\Delta E_5 = \Delta H(\mathbf{12}) - \Delta H(\mathbf{13}) = 95.07$
14	59.69	$\Delta E_6 = \Delta H(\mathbf{12}) - \Delta H(\mathbf{14}) = -62.64$

respectively). These results explain the formation of the bis-alkylated **4** and **7** as sole products from the reaction of **1** or **3** and **6** with bromoethanol (**2**) or chloropropanol (**5**) in presence of potassium carbonate in boiling DMF.

In contrast, the energy difference between the mono-alkylated **12** and its corresponding imidazo-thiazine ($\Delta E_6 = -62.64$ Kcal.mol^{-1}) is lower than that between **12** and the bis-alkylated **13** ($\Delta E_5 = 95.07$ Kcal.mol^{-1}). On the basis of these results, one could predict that the imidazo-thiazine **14** was favored to be formed rather than the bis-alkylated product but the higher stability of **12** has altered the energetic behavior of this reaction where both of the bis-alkylated analogue **13** and the imidazo-thiazine **14** were formed. These conclusions were in agreement with the experimental results.

CONCLUSIONS

A regioselective alkylation of 4,5-diphenylimidazole-2-thiol (**1**) with hydroxyl-alkylating agents in the presence of NaOEt or NaOAc has been achieved successfully to give only the respective S-alkylated derivatives, via the formation of the sodium salt of the thiolate anion generated by proton abstraction from the thiol group. Further alkylation of the S-alkylated analogues in boiling DMF and in the presence of potassium carbonate afforded the acyclonucleoside analogues. This could presumably be due to the ability of K_2CO_3 to abstract the proton from NH group which is not the case with NaOEt or NaOAc. These conditions were used to develop a general method for the synthesis of the fused imidazo-thiazines or thiazolines via the cyclization of **4**, **6**, and **12** with K_2CO_3 /DMF.

A comparison of the results from using MWI with that under conventional method revealed that higher yields were obtained in shorter times. Better results were obtained when bentonite was used as solid support. Thus, economical and environmental impacts can be achieved when the MW irradiation was combined with the solid support. The results were supported by the semiemoerical AM1 theoritical calculations.

EXPERIMENTAL

General Procedures

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 spot 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. The NMR spectra were recorded on Jeol spectrometer (500 MHz). Chemical shifts δ are given in ppm relative to

the signal for TMS as internal standard. The double quatum filtered-correlation spectroscopy DQF-COSY and heteronuclear multiple quantum correlation HMQC experiments were used to confirm the spectral analysis. The elemental analyses were performed by the microanalysis unit at the Faculty of Science, Cairo University.

General Procedure for the Alkylation 4,5-Diphenylimidazole-2-thione (1)

Conventional Method (CM). To a solution of compound **1**, **3**, **6**, **9**, or **12** (1 mmol) in a solvent (15 mL) and base (1.1 or 2.2 mmol), the appropriate hologeno-ethanols **2** or **3**, chloroglycerol **11**, and 2,3-*O*-isopropylidene-1-*O*-(*p*-tolylsulfonyl)-glycerol (**8**) (1.1 mmol or 2.2 mmol) were added with stirring. The conditions of the reaction are shown in Table 1. The reaction mixture was poured onto crushed ice. The products were washed with water, dried, and recrystallized from ethanol.

Microwave Method (MW). A mixture of compound **1**, **3**, **6**, **9**, or **12** (0.36 mmol), solvent (3 mL), base (0.36 or 0.73 mmol), and the appropriate alkylating agents (0.33 mmol or 0.73 mmol) were placed in a closed Teflon vessel and then irradiated by MW. The reaction mixture was processed as described above (Table 1).

Microwave and Solid Support Method. A mixture of **1**, **3**, **6**, **9**, or **12** (0.36 mmol) and an appropriate alkylating agent (0.36 mmol or 0.73 mmol) and bentonite (0.3 g) were mixed uniformly. The mixture was placed in a closed Teflon vessel and then irradiated by MW for 1–3 minutes. After cooling the products were extracted by boiled ethanol and were recrystallized from ethanol.

2-[(2-Hydroxyeth-1-yl)thio]-4,5-diphenyl-1*H*-imidazole (3). This compound was obtained as colorless crystals, m.p: 168–170°C, IR (KBr): 3087 (CH-Ar), 3413 (OH). ^{1}H NMR (DMSO-d_6) δ: 3.17 (dd, 2H, $J = 6.1$ Hz, $J = 6.9$ Hz, SCH_2), 3.67 (ddd, 2H, $J = 6.1$ Hz, $J = 6.9$ Hz, $J = 11.9$ Hz, CH_2O), 5.13 (br, 1H, D_2O exchangeable, OH), 7.15–7.43 (m, 10H, Ar-H), 12.54 (s, 1H, D_2O exchangeable, NH). *Anal. Calcd.* for $C_{17}H_{16}N_2OS$ (296.10): C, 68.89; H, 5.44; N, 9.45. Found: C, 68.79; H, 5.65; N, 9.25.

1-(2-Hydroxyeth-1-yl)-2-[(2-hydroxyeth-1-yl)thio]-4,5-diphenylimidazole (4). This compound was obtained as colorless crystals; m.p: 119–120°C, IR (KBr): 3410 (OH). ^{1}H NMR (DMSO-d_6) δ: 3.12 (br, 1H, D_2O exchangeable, OH), 3.24 (t, 2H, $J = 4.6$ Hz, SCH_2), 3.65 (dd, 2H, $J = 5.3$ Hz, $J = 6.1$ Hz, NCH_2), 3.97 (dd, 2H, $J = 5.3$ Hz, $J = 6.1$ Hz, CH_2O), 4.05 (t, 2H, $J = 4.6$ Hz, CH_2O), 4.42 (br, 1H, D_2O exchangeable, OH), 7.15–7.43 (m, 10H, Ar-H). *Anal. Calcd.* for $C_{19}H_{20}N_2O_2S$ (340.12): C, 67.03; H, 5.92; N, 8.23. Found: C, 66.97; H, 5.61; N, 8.03.

2-[(3-Hydroxyprop-1-yl)thio]-4,5-diphenyl-1*H*-imidazole (6). This compound was obtained as colorless crystals; m.p: 158–160°C, IR (KBr): 1585

(C = C), 3059 (CH-Ar), 3390 cm^{-1} (OH). ^1H NMR (DMSO-d_6) δ: 1.74–1.79 (m, 2H, $CH_2CH_2CH_2$), 3.12 (t, 2H, J = 6.9 Hz, SCH_2), 3.49 (t, 2H, J = 6.1 Hz, CH_2O), 4.72 (br, 1H, D_2O exchangeable, OH), 7.20–7.32 (m, 10H, Ar-H), 12.55 (s, 1H, D_2O exchangeable, NH). *Anal. Calcd.* for $C_{18}H_{18}N_2OS$ (310.11): C, 69.65; H, 5.84; N, 9.02. Found: C, 69.76; H, 6.03; N, 8.67.

1-(3-Hydroxyprop-1-yl)-2-[(3-hydroxyprop-1-yl)thio]-4,5-diphenylimidazole (7). This compound was obtained as yellow crystals, m.p: 145°C; IR (KBr): 3438 (OH). ^1H NMR (DMSO-d_6) δ: 1.54–1.59 (m, 2H, $SCH_2CH_2CH_2$) 1.82–1.85 (m, 2H, $NCH_2CH_2CH_2$), 3.19–3.22 (m, 4H, SCH_2, NCH_2), 3.50–3.52 (m, 2H, CH_2O), 3.76–3.79 (m, 2H, CH_2O), 4.46–4.49 (br, 1H, D_2O exchangeable, OH), 4.68–4.71 (br, 1H, D_2O exchangeable, OH), 7.05–7.47 (m, 10H, Ar-H). *Anal. Calcd.* for $C_{21}H_{24}N_2O_2S$ (368.16): C, 68.45; H, 6.56; N, 7.60. Found: C, 68.32; H, 6.43; N, 7.89.

2-[(2,3-*O*-Isopropylidene-2,3-dihydroxyprop-1-yl)thio]-4,5-diphenyl-1*H*-imidazole (9). This compound was obtained as colorless crystals; m.p: 159–160°C, IR (KBr): 3022 cm^{-1} (C-H Ar). ^1H NMR ($CDCl_3$) δ: 1.40, 1.44 (2 s, 6H, 2 × CH_3), 3.20 (dd, 1H, J = 6.9 Hz, J = 14.5 Hz, SCH_2), 3.27 (dd, 1H, J = 4.6 Hz, J = 14.5 Hz, SCH_2), 3.80 (dd, 1H, J = 7.7 Hz, J = 8.4 Hz, CH_2O), 4.16 (dd, 1H, J = 6.1 Hz, J = 8.4 Hz, CH_2O), 4.48–4.50 (m, 1H, CHO), 7.26–7.48 (m, 10H, Ar-H) 12.60 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR ($CDCl_3$) δ: 25.7 (CH_3), 26.8 (CH_3), 36.8 (SCH_2), 68.4 (CH_2O), 77.1 (CHO), 110.1 ($C(CH_3)_2$), 127.6, 128.7, 140.14 (Ar-C). *Anal. Calcd.* for $C_{21}H_{22}N_2O_2S$ (366.14): C, 68.82; H, 6.05; N, 7.64. Found: C, 68.50; H, 6.22; N, 7.98.

1-(2,3-*O*-Isopropylidene-2,3-dihydroxyprop-1-yl)-2-[(2,3-*O*-isopropylidene-2,3-dihydroxyprop-1-yl)thio]-4,5-diphenylimidazole (10). This compound was obtained as colorless crystals, m.p: 180–182°C; ^1H NMR (DMSO-d_6) δ: 1.19, 1.20, 1.21, 1.27 (4 s, 12H, 4 × CH_3), 3.39 (dd, 2H, J = 3.1 Hz, J = 9.2 Hz, SCH_2), 3.73 (dd, 1H, J = 2.3 Hz, J = 5.3 Hz, J = 9.2, CH_2O(a)), 3.90 (dd, 1H, J = 5.3Hz, J = 9.2, CH_2O(b)), 3.99–4.09 (m, 2H, 2 × CH_2O(a), CH_2O(b)), 4.21 (dd, 1H, J = 5.3 Hz, J = 14.5 Hz, NCH_2), 4.28–4.32 (m, 1H, NCH_2), 4.33–4.46 (m, 2H, 2 x CHO), 7.18–7.41 (m, 10H, Ar-H). *Anal. Calcd.* for $C_{27}H_{32}N_2O_4S$ (480.21): C, 67.47; H, 6.71; N, 5.83. Found: C, 67.68; H, 6.91; N, 5.90.

2-[(2,3-Dihydroxyprop-1-yl)thio]-4,5-diphenyl-1*H*-imidazole (12). This compound was obtained as colorless crystals; m.p: 148°C, IR (KBr): 3096 (C-H Ar), 3314 (br OH). ^1H NMR (DMSO-d_6) δ: 3.14 (dd, 1H, J = 6.1 Hz, J = 13.7 Hz, SCH_2), 3.31 (dd, 1H, J = 6.1 Hz, J = 13.7 Hz, SCH_2), 3.35–3.43 (m, 2H, CH_2O), 3.72–3.75 (m, 1H, CHO), 4.98 (t, 1H, J = 5.3 Hz, D_2O exchangeable, OH), 5.45 (br, 1H, D_2O exchangeable, OH), 7.15–7.43 (m, 10H, Ar-H), 12.61 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ: 37.2 (SCH_2), 64.5 (CH_2O), 71.8 (CHO), 127.2, 127.4, 128.2, 128.8, 129.2,

131.1, 135.1, 137.2 (Ar-C). *Anal. Calcd.* for $C_{18}H_{18}N_2O_2S$ (326.11): C, 66.23; H, 5.56; N, 8.58. Found: C, 65.98; H, 5.86; N, 8.41.

1-(2,3-Dihydroxyprop-1-yl)-2-[(2,3-dihydroxyprop-1-yl)thio-4,5-diphenylimidazole (13). This compound was obtained as colorless needless after purification by column chromatography using EtOAc-Hexane (40–60) as eluant; m.p: 125–126°C; IR (KBr): 1565 (C = C), 1610 (C = N), 3463 (OH). ^{1}H NMR (DMSO-d_6) δ: 3.20 (ddd, 1H, J = 5.4 Hz, J = 7.7 Hz, J = 10.7 Hz, SCH_2), 3.33–3.43 (m, 5H, SCH_2, 2 × CH_2O), 3.68–3.75 (m, 1H, CHO), 3.84–3.90 (m, 1H, CHO), 4.05 (dd, 1H, J = 8.4 Hz, J = 14.5 Hz, NCH_2), 4.24 (dd, 1H, J = 3.8 Hz, J = 14.5 Hz, NCH_2), 4.80 (t, 1H, J = 6.1 Hz, D_2O exchangeable, OH), 4.90 (t, 1H, J = 6.2 Hz, D_2O exchangeable, OH), 5.17 (d, 1H, J = 4.5 Hz, D_2O exchangeable, OH), 5.21 (dd, 1H, J = 3.1 Hz, J = 5.3 Hz, D_2O exchangeable, OH), 7.16–7.45 (m, 10H, Ar-H). *Anal. Calcd.* for $C_{21}H_{24}N_2O_4S$ (400.15): C, 62.98; H, 6.04; N, 6.99. Found: C, 63.19; H, 5.95; N, 6.68.

Deisopropylidenation of 9 and 10. General procedure. The isopropylidenes **9** and **10** (5 mmol) were 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 products were collected and crystallized from ethanol to give **12** and **13**, respectively. The products were identical with those prepared by the above method.

Isopropylidenation of 12 and 13. General procedure. Compound **12** and **13** (0.25 mmol) were 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 products **9** and **10** were crystallized from ethanol or purified by column chromatography to give identical products with those obtained by the above alkylation method.

General Procedure for the Synthesis of Imidazothiazines and Thiazole

Conventional method (CM). A mixture of **3**, **7**, or **12** (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.

Microwave Method (MW). A mixture of **6**, **7**, or **12** (0.33 mmol) and potassium carbonate (0.5 mmol) in DMF (3 mL) in a closed Teflon vessel was irradiated by MWI. The obtained reaction mixture was treated as described above (Table 1).

6,7-Diphenyl-2*H*,3*H*,4*H*-3-hydroxy-tetrahydroimidazo[2,1-*b*][1,3]thiazine (14). This compound was obtained as colorless crystals, m.p: 210–212°C; IR (KBr): 3269 cm^{-1} (OH). ^{1}H NMR (DMSO-d_6) δ: 3.11 (dd, 1H, J = 2.3

Hz, $J = 12.6$ Hz, SCH_2), 3.26 (dd, 1H, $J = 6.3$ Hz, $J = 13.0$ Hz, SCH_2), 3.55 (dd, 1H, $J = 6.5$ Hz, $J = 12.6$ Hz, NCH_2), 3.76 (dd, 1H, $J = 3.4$ Hz, $J = 12.6$ Hz, NCH_2), 4.26–4.30 (m, 1H, CHO), 5.61 (br, 1H, D_2O exchangeable OH), 7.18–7.41 (m, 10H, Ar-H). *Anal. Calcd.* for $C_{18}H_{16}N_2S$ (308.40): C, 70.10; H, 5.23; N, 9.08. Found: C, 69.92; H, 5.39; N, 9.36.

5,6-Diphenyl-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole (15). This compound was obtained as colorless plates, m.p: 232–234°C; ^{1}H NMR (DMSO-d_6) δ: 3.82 (t, 2H, $J = 8.4$, SCH_2), 4.10 (t, 2H, $J = 8.4$, NCH_2), 7.15–7.23 (m, 2H, Ar-H), 7.34–7.40 (m, 5H, Ar-H), 7.49–7.54 (m, 3H, Ar-H). *Anal. Calcd.* for $C_{17}H_{14}N_2S$ (278.37): C, 73.35; H, 5.07; N, 10.06. Found: C, 73.21; H, 4.93; N, 10.19.

6,7-Diphenyl-2*H*,3*H*,4*H*-tetrahydroimidazo[2,1-*b*][1,3]thiazine (16). This compound was obtained as colorless plates, m.p: 272°C; ^{1}H NMR (DMSO-d_6) δ: 1.92–1.95 (m, 2H, $CH_2CH_2CH_2$), 3.46 (t, 2H, $J = 6.1$, SCH_2), 3.83 (t, 2H, $J = 5.3$, NCH_2), 7.15–7.23 (m, 2H, Ar-H), 7.34–7.40 (m, 5H, Ar-H), 7.49–7.54 (m, 3H, Ar-H). *Anal. Calcd.* for $C_{18}H_{16}N_2S$ (292.40): C, 73.94; H, 5.52; N, 9.58. Found: C, 74.07; H, 5.83; N, 9.39.

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