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FACILE NOVEL SYNTHESIS AND REACTIONS OF THIAZOLIDIN-4-ONE DERIVATIVES FOR ANTIMICROBIAL AGENTS

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A facile and fast procedure for synthesis of 3-phenyl-cyclohexane(1′-2)thiazolidin-4-one (1), which underwent condensation with glucose and* p-*chlorobenzaldehyde to afford 2 and 3, respectively. Compound 3 was used as precursor for the preparation of some fused heterocyclic compounds 4–7. Compound 4 was alkylated using dichloroacetone and chloroacetic acid to afford 8 and 9, respectively. Also, it reacted with acrylonitrile and hydrazine hydrate to afford 10 and 11, respectively. Compound 9 was condensed with* p-*chlorobenzaldehyde and glucose to afford 12 and 13, respectively. Selected members of the synthesized compounds were screened for antimicrobial activity.

Keywords: Antimicrobial activities; bis-thiazolopyrimidine; pyrazolothiazole; thiazolopyridine; thiazolopyrimidine

INTRODUCTION

Thiazolidin-4-one derivatives exhibit high activity in vitro against mycobacterium tuberculosis (TB) and as drugs to treat HIV and cancer.[1–3] Recently, 2-aryl-4-thiazolidinone has been synthesized and found to exhibit potent selective antiplatelet activating factors both in vitro and in vivo and anti-inflammatory,[4] antibacterial, anticancer,[5] and anti-HIV-1 activities.[6] Spiroheterocyclic compounds including thiazolidine moiety have antimicrobial activity.[7] Both pyrazolothiazole and thiazolopyrimidine moieties have potent kinase modulators[8] and are used in pharmaceutical compositions.[9] The latter compound has analgesic and anti-Parkinson activities[10] and inhibits the growth of parasite *Trypanosoma cruzi*.[11] In continuation of our search of new compounds with anticipated biological activity starting from accessible material,[12–19] we aimed to obtain new compounds of the fused thiazole system, which are expected to possess notable chemical and biological activities.

RESULTS AND DISCUSSION

We have synthesized 3-phenyl-cyclohexane(1′-2)thiazolidin-4-one (**1**) in good yield via a one-pot reaction to afford white crystals (cf. the Experimental section;

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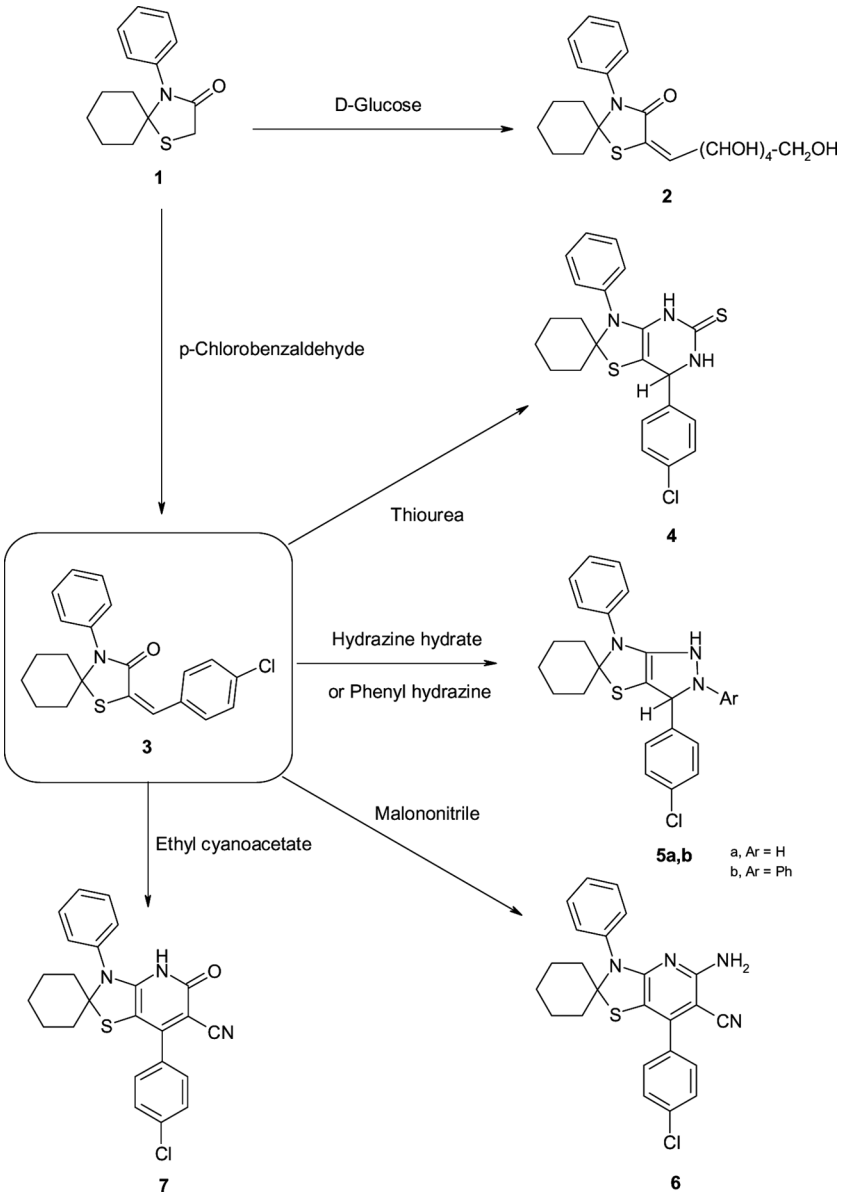
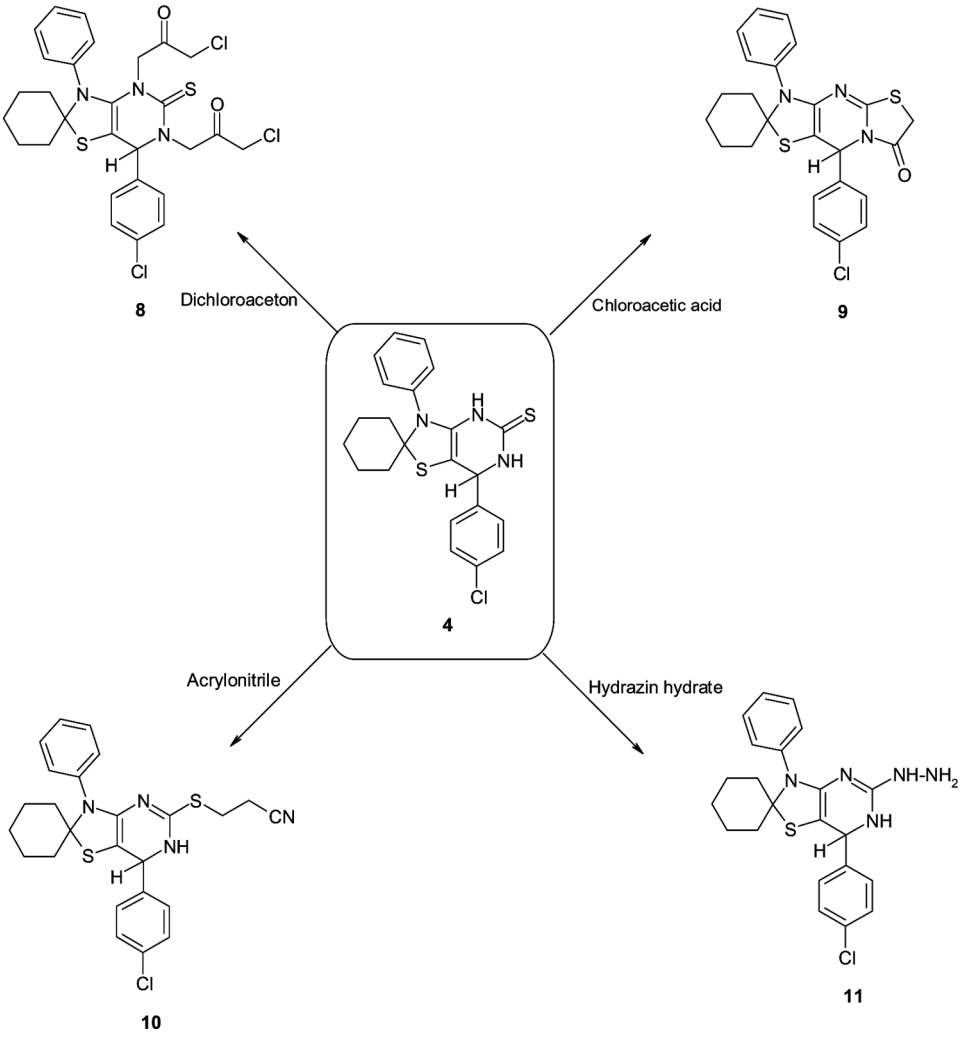


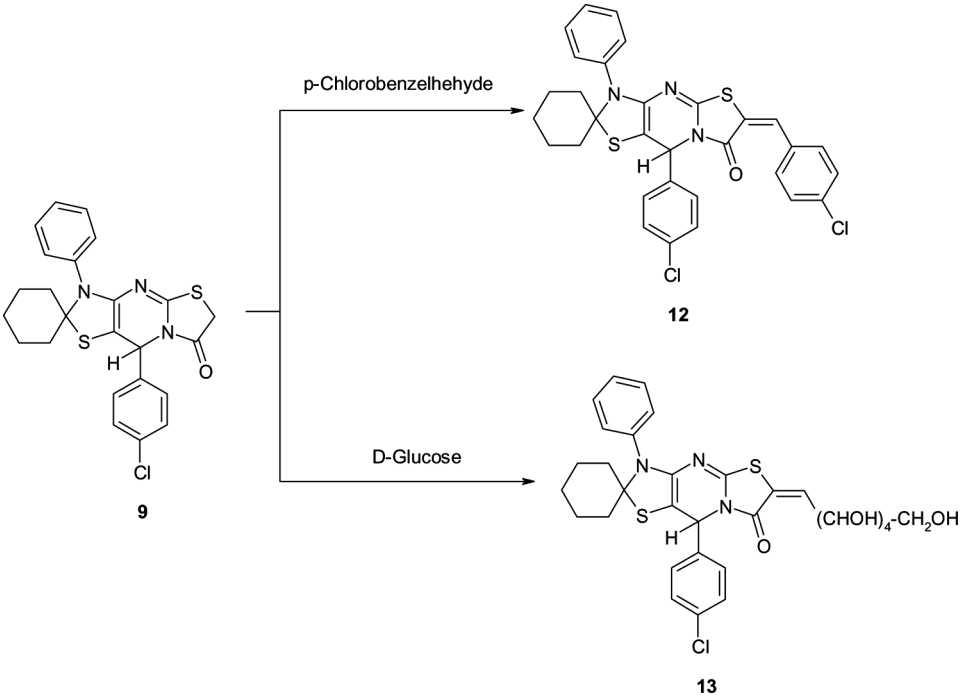
Scheme 1. Condensation and Michael reaction of thiazlidine with different reagents.

Scheme 1). The assigned structure was proved based on elemental and spectral analysis. The infrared (IR) spectrum of the isolated product showed absorption bands at 1713 cm^{-1} corresponding to the (CO) group. The ^1H NMR spectrum revealed signals at δ 1.3 ppm and δ 1.8 ppm attributed to cyclohexane protons, signals at δ 3.40 ppm attributed to thiazole ring protons, and a multiplet at δ 7.0–7.3 ppm corresponding to aromatic protons. Furthermore, the mass spectra gave a molecular

ion peak at m/z 247.1. Also, compound **1** was confirmed chemically via condensation with D-glucose and *p*-chlorobenzaldehyde to afford **2** and **3**, respectively. The structures of the latter compounds were elucidated from their correct data (cf. the Experimental section). For example, the IR spectrum of compound **3** showed an absorption band at 1687 cm^{-1} (CO) due to conjugation, ^1H NMR spectrum showed absence of thiazolomethylene protons, and its mass spectrum showed the M^+ peak at 369.3, all of which support its molecular formula. Compound **3** was used as starting material for further syntheses of other heterocyclic compounds. It reacted with thiourea, hydrazine hydrate derivatives, malononitrile, and ethyl cyanoacetate to afford compounds **4–7**, respectively (Scheme 1). The structures of these compounds were confirmed from their correct data (cf. the Experimental section).



Scheme 2. Alkylation and disulfurization of thiazolopyrimidine.



Scheme 3. Condensation of bis-thiazolopyrimidine with aldehyde and glucose.

For example, the IR spectrum of compound **4** showed the absence of the band characteristic for (CO) and the presence of absorption bands at 3120, 3170 cm^{-1} (NH), and 1213 cm^{-1}(CS). Also, its ^1H NMR spectrum revealed signals at δ 4.60 ppm characteristic of the pyrimidine ring and at δ 8.90 and 11.20 ppm for 2NH protons that are D_2O exchangeable. Mass spectra showed M^+ at 427.3, which supports its molecular formula (cf. the Experimental section; Scheme 1).

On the other hand, compound **4** was allowed to react with halo compounds, namely dichloroacetone and/or chloroacetic acid, to afford compounds **8** and **9**, respectively. Also, compound **4** was reacted with acrylonitrile via Michael addition to afford **10**, and its reaction with hydrazine hydrate afforded hydrazino pyrimidine derivative **11** (Scheme 2).

Finally, bis-thiazolopyrimidine derivative **9** was condensed with *p*-chlorobenzaldehyde and D-glucose to afford **12** and **13**, respectively. The structures of all compounds were confirmed by their correct data (cf. the Experimental section; Scheme 3).

Antimicrobial Activity

Some of the synthesized compounds **4, 6, 7, 10**, and **15** were tested in concentrations of 0.1 g/ml using dimethylformamide (DMF) as a solvent. The microorganisms used were as follows: Gram-negative bacteria, *E. coli* and *P. aeruginosa*; Gram-positive bacteria, *B. subtilis*, *S. aureus*, and *S. lutea*; and yeast, *C. albicans.*

Medium

The cap-assay method containing (g/l) peptone (6.0), yeast extract (3.0), meat extract (1.5), glucose (1.0), and agar (20.0) were used. The medium was sterilized and divided while hot (50–60 °C) into 15-ml portions among sterile Petri dishes 9 cm in diameter. One ml of the spore suspension of each microorganism was spread all over the surface of the cold solid medium placed in the Petri dish.

Method[20]

Portions of 0.5 g of each tested compound were dissolved in 5 ml of DMF. An amount of 0.1 ml of the test solution was placed on Whatman paper disc, 9 mm in diameter, and the solvent was left to evaporate. These saturated discs were placed carefully on the surface of the inoculated solid medium; each Petri dish contained at least three discs. The Petri dishes were incubated at 5 °C for an hour to permit good diffusion, then transferred to an incubator at 85 °C overnight, and then examined. The results were recorded by measuring the inhibition zone diameters.

CONCLUSION

The results of antimicrobial activity of compounds **1, 4, 5a, 6**, and **13** showed interesting degrees of antibacterial activity. Penicillin was used as a reference to evaluate the potency of the tested compounds. Compounds **1, 4, 5a, 6**, and **13** showed greater antibacterial activities than the standard drug (penicillin). Compound **7** did not show any activity against the tested microorganisms, whereas compounds **6** and **11** showed greater activity against *C. albicans* than the standard drug (nystatin). These results of biological activities encourage further work on such ring system (Table 1).

Table 1. Antimicrobial activities of the tested compounds

Tested compounds and standards	Inhibition zone (mm)					
	Gram-negative bacteria		Gram-positive bacteria			Yeast
	E. coli.	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*S. lutea*	*C. albicans*
Pencillin	15	13	20	15	17	—
Nystalin	—	—	—	—	—	15
1	16	20	20	—	25	—
4	17	20	18	10	25	—
5a	18	15	15	12	20	—
6	15	20	20	10	—	20
7	—	—	—	—	—	—
11	—	—	—	—	—	25
13	17	22	22	—	24	—

Notes. Highly sensitive: inhibition zone 21–30 mm.
Fairly sensitive: inhibition zone 16–20 mm.
Slightly sensitive: inhibition zone 10–15 mm.

EXPERIMENTAL

All melting points are uncorrected and measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). Infrared (IR) spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Shimadzu) at the National Research Centre, Cairo, Egypt. ^{1}H NMR spectra were determined on a Jeol-Ex-300 NMR spectrometer, and chemical shifts were expressed as part per million (ppm; δ values) against tetramethylsilane (TMS) as internal reference. Mass spectra (MS) were recorded on EI +Q1 MSLMR UPLR, at the National Research Centre, Cairo, Egypt. Microanalyses were operated using a Mario El Mentar apparatus at the Organic Microanalysis Unit, National Research Centre, Cairo, Egypt, and the results were within the accepted range (±0.20) of the calculated values.

3-Phenyl-cyclohexane(1′-2)thiazolidin-4-one (1)

A mixture of aniline (1.86 mL, 20 mmol), cyclohexanone (1.96 mL, 20 mmol), and 2-mercaptoacetic acid (1.96 mL, 20 mmol) in 50 mL dry benzene was refluxed for 8 h. The solvent was evaporated under reduced pressure. The formed solid was filtered off, dried, and recrystallized from ethanol to afford compound **1** in 56% yield; mp 166–167 °C. IR spectrum (KBr, ν, cm^{-1}): 1713 (CO); ^{1}H NMR spectrum ($CDCl_3$, δ ppm):1.30 (t, $J = 3.50$ Hz, 6H, $3CH_2$), 1.80 (t, $J = 2.40$ Hz, 4H, $2CH_2$), 3.40 (s, 2H, thiazole H), 7.00–7.30 (m, 5H, Ar-H); MS, m/z (%): 247.1 (M^+, 35). Analysis for $C_{14}H_{17}NOS$ (247.36) required: C, 67.98; H, 6.93; N, 5.66; S, 12.96; found: C, 67.95; H, 6.90; N, 5.58; S, 13.00.

5-(2,3,4,5,6-Pentahydroxy-hexylidene)-3-phenyl-cyclohexane(1′-2) thiazolidin-4-one (2)

Compound **1** (1.23 gm, 5 mmol) in absolute ethanol (30 mL) and few drops of acetic acid were added to a solution of D-glucose (0.83 g, 5 mmol) in water (0.5 mL) with stirring at 60 °C for 5 h. The product that separated out of cooling was filtered off, washed with water followed by ethanol, and dried to afford compound **2** in 60% yield; mp 149–150 °C. IR spectrum (KBr, ν, cm^{-1}): 3410 (OH), 1700 (CO); ^{1}H NMR spectrum ($CDCl_3$, δ ppm):1.29 (t, $J = 3.45$ Hz, 6H, $3CH_2$), 1.78 (t, $J = 2.43$ Hz, 4H, $2CH_2$), 3.30–3.95 (m, 6H, glucose), 4.60–4.90 (m, 5H, OH, D_2O exchangeable), 6.60 (d, $J = 1.68$ Hz, 1H, methylene), 7.00–7.70 (m, 5H, Ar-H). Analysis for $C_{20}H_{27}NO_6S$ (409.5) required: C, 58.66; H, 6.65; N, 3.42; S, 7.83; found: C, 58.72; H, 6.70; N, 3.46; S, 7.90.

5-(4-Chloro-benzylidene)-3-phenyl-cyclohexane(1′-2) thiazolidin-4-one (3)

A mixture of compound **1** (1.23 g, 5 mmol) and 4-chlorobenzaldehyde (0.7 ml, 5 mmol) was refluxed in a mixture of glacial acetic acid and acetic anhydride (3:1) containing anhydrous sodium acetate (0.36 g, 5 mmol) for 3 h. The reaction mixture was cooled and poured gradually with stirring into cool water (100 mL). The formed solid was filtered off, dried, and recrystallized from methanol to give compound **3** in

65% yield; mp 189–190 °C. IR spectrum (KBr, ν, cm^{-1}): 1687 (CO); ^1H NMR spectrum ($CDCl_3$, δ ppm):1.28 (t, $J = 3.30$ Hz, 6H, $3CH_2$), 1.76 (t, $J = 2.36$ Hz, 4H, $2CH_2$), 7.20–7.70 (m, 10H, Ar-H +methylene H); MS, m/z (%): 369.3 (M^+, 17). Analysis for $C_{21}H_{20}ClNOS$ (369.91) required: C, 68.19; H, 5.45; Cl, 9.58; N, 3.79; S, 8.67; found: C, 68.25; H, 5.42; Cl, 9.64; N, 4.00; S, 8.72.

7-(4-Chloro-phenyl)-3-phenyl-2,3,6,7-tetrahydro-cyclohexane(1′-2) thiazolo[4,5-d]pyrimidine-5-thione (4)

A mixture of compound **3** (1.88 g, 5 mmol) and thiourea (0.76 g, 10 mmol) was refluxed in ethanolic sodium hydroxide (1 g, 30 ml) for 4 h. The reaction mixture was cooled and poured into water (100 ml). The formed solid was filtered off, dried, and recrystallized from dioxane to give compound **4** in 56% yield; mp 273–274 °C. IR spectrum (KBr, ν, cm^{-1}): 3170, 3120 (2NH), 1213 (CS); ^1H NMR spectrum (DMSO-d_6, δ ppm):1.28 (t, $J = 3.18$ Hz, 6H, $3CH_2$), 1.72 (t, $J = 2.20$ Hz, 4H, $2CH_2$), 4.60 (s, 1H, pyrimidine H), 6.50–7.20 (m, 9H, Ar-H), 8.90 (s, 1H, NH, D_2O exchangeable), 11.20 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 427.3 (M^+, 19). Analysis for $C_{22}H_{22}ClN_3S_2$ (428.02) required: C, 61.74; H, 5.18; Cl, 8.28; N, 9.82; S, 14.98; found: C, 61.52; H, 5.20; Cl, 8.30; N, 9.90; S, 14.76.

3-(4-Chloro-phenyl)-3-phenyl-2,3,6,7-tetrahydro-cyclohexane(1′-5) pyrazolo[3,4-d]thiazole (5a)

A mixture of compound **3** (1.88 g, 5 mmol) and hydrazine hydrate (0.40 mL, 10 mmol) was refluxed in absolute ethanolic (30 ml) for 4 h. The solid substance was filtered off, dried, and recrystallized from dioxane to give compound **5a** in 80% yield; mp 209–210 °C. IR spectrum (KBr, ν, cm^{-1}): 3100, 3118 (2NH); ^1H NMR spectrum (DMSO-d_6, δ ppm):1.30 (t, $J = 3.25$ Hz, 6H, $3CH_2$), 1.80 (t, $J = 2.32$ Hz, 4H, $2CH_2$), 4.70 (s, 1H, pyrazole H), 6.60–7.30 (m, 9H, Ar-H), 9.20 (s, 1H, NH, D_2O exchangeable), 10.50 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 383.2 (M^+, 28). Analysis for $C_{21}H_{22}ClN_3S$ (383.94) required: C, 65.69; H, 5.78; N, 10.94; S, 8.35; found: C, 66.30; H, 5.81; N, 11.00; S, 8.55.

3-(4-Chloro-phenyl)-2,3-diphenyl-2,6,7-trihydro-cyclohexane(1′-5) pyrazolo[3,4-d]thiazole (5b)

A mixture of compound **3** (1.88 g, 5 mmol) and phenyl hydrazine (1.06 mL, 10 mmol) was refluxed in absolute ethanolic (50 ml) for 4 h. The reaction mixture was cooled, and the solid substance was filtered off, dried, and recrystallized from dioxane to give compound **5b** in 80% yield; mp 263–264 °C. IR spectrum (KBr, ν, cm^{-1}): 3150 (NH); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.29 (t, $J = 3.20$ Hz, 6H, $3CH_2$), 1.75 (t, $J = 2.24$ Hz, 4H, $2CH_2$), 4.58 (s, 1H, pyrazole H), 6.50–7.20 (m, 14H, Ar-H), 9.40 (s, 1H, NH, D_2O exchangeable; MS, m/z (%): 459.4 (M^+, 35). Analysis for $C_{27}H_{26}ClN_3S$ (460.03) required: C, 70.49; H, 5.70; N, 9.13; S, 6.97; found: C, 70.53; H, 5.62; N, 9.10; S, 7.00.

5-Amino-7-(4-chloro-phenyl)-3-phenyl-2,3-dihydro-cyclohexane(1′-2) thiazolo[4,5-b]pyridine-6-carbonitrile (6)

A mixture of compound **3** (1.88 g, 5 mmol), malononitrile (0.66 g, 10 mmol), and ammonium acetate (1.53 g, 20 mmol) was refluxed in glacial acetic acid (40 ml) for 30 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **6** in 50% yield; mp 222–223 °C. IR spectrum (KBr, ν, cm^{-1}): 3417–3220 (NH_2), 2216 (CN); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.28 (t, $J = 3.24$ Hz, 6H, $3CH_2$), 1.72 (t, $J = 2.60$ Hz, 4H, $2CH_2$), 6.50–7.50 (m, 9H, Ar-H), 7.80 (s, 2H, NH_2, D_2O exchangeable); MS, m/z (%): 432.3 (M^+, 90). Analysis for $C_{24}H_{21}ClN_4S$ (432.94) required: C, 66.58; H, 4.89; N, 12.94; S, 7.41; found: C, 66.60; H, 4.93; N, 13.00; S, 7.46.

7-(4-Chloro-phenyl)-5-oxo-3-phenyl-2,3,4,5-tetrahydro-cyclohexane(1′-2)thiazolo[4,5-b]pyridine-6-carbonitrile (7)

A mixture of compound **3** (1.88 g, 5 mmol), ethyl cyanoacetate (1.13 g, 10 mmol), and anhydrous ammonium acetate (1.60 g, 20 mmol) was refluxed in glacial acetic acid (40 ml) for 20 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from acetic acid to give compound **7** in 55% yield; mp 251–252 °C. IR spectrum (KBr, ν, cm^{-1}): 3150 (NH), 2222 (CN), 1687 (CO); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.29 (t, $J = 3.33$ Hz, 6H, $3CH_2$), 1.76 (t, $J = 2.23$ Hz, 4H, $2CH_2$), 6.60–7.30 (m, 9H, Ar-H), 10.20 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 433.5 (M^+, 83). Analysis for $C_{24}H_{20}ClN_3OS$ (433.95) required: C, 66.43; H, 4.65; N, 9.68; S, 7.39; found: C, 66.50; H, 4.66; N, 9.73; S, 7.42.

1-Chloro-3-[6-(3-chloro-2-oxo-propyl)-7-(4-chloro-phenyl)-3-phenyl-5-thioxo-3,5,6,7-tetrahydro-cyclohexane(1′-2) thiazolo[4,5-d]pyrimidin-4-yl]-propan-2-one (8)

A mixture of compound **4** (1.67 g, 2.5 mmol) and dichloroacetone (0.73 g, 50 mmol) was refluxed in ethanolic sodium hydroxide (0.4 g, 30 ml) for 3 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from ethanol to give compound **8** in 70% yield; mp 182–183 °C. IR spectrum (KBr, ν, cm^{-1}): 1703, 1709 (CO), 1202 (CS); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.28 (t, $J = 3.24$ Hz, 6H, $3 \times CH_2$), 1.74 (t, $J = 2.32$ Hz, Hz, 4H, $2CH_2$), 4.52 (s, 4H, $2CH_2$), 4.58 (s, 1H, pyrimidine), 6.30 (s, 4H, $2CH_2$), 6.50–7.20 (m, 9H, Ar-H); MS, m/z (%): 607 (M^+, Cl^{35}, 33), 609 (M^+, Cl^{37}, 27). Analysis for $C_{28}H_{28}Cl_3N_3O_2S_2$ (609.03) required: C, 55.22; H, 4.63; N, 6.90; S, 10.53; found: C, 55.00; H, 4.65; N, 7.00; S, 10.65.

9-(4-Chloro-phenyl)-3-phenyl-3,9-dihydro-cyclohexane(1′-2) bisthiazolo[3,2-a;4′,5′-d]pyrimidin-7-one (9)

A mixture of compound **4** (1.67 g, 2.5 mmol) and chloroacetic acid (0.26 g, 2.5 mmol) was refluxed in a mixture of glacial acetic acid and acetic anhydride

(3:1) containing anhydrous sodium acetate (0.18 g, 2.5 mmol) for 3 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **9** in 75% yield; mp 182–183 °C. IR spectrum (KBr, ν, cm^{-1}): 1703 (CO); ^1H NMR spectrum ($CDCl_3$, δ ppm):1.29 (t, $J = 3.28$ Hz, 6H, $3CH_2$), 1.76 (t, $J = 2.32$ Hz, 4H, $2CH_2$), 3.40 (s, 2H, thiazolone), 5.60 (s, 1H, pyrimidine), 6.50–7.30 (m, 9H, Ar-H); MS, m/z (%): 467.1 (M^+, 30). Analysis for $C_{24}H_{22}ClN_3OS_2$ (468.04) required: C, 61.59; H, 4.74; N, 8.98; S, 13.70; found: C, 61.38; H, 4.76; N, 9.00; S, 13.75.

3-[7-(4-Chloro-phenyl)-3-phenyl-2,3,6,7-tetrahydro-cyclohexane (1′-2)thiazolo[4,5-d]pyrimidin-5-ylsulfanyl]-propionitrile (10)

A mixture of compound **4** (1.67 g, 2.5 mmol) and acrylonitrile (0.13 mL, 2.5 mmol) was refluxed in absolute ethanol (30 mL) for 3 h. The formed solid was filtered off, dried, and recrystallized from ethanol to give compound **10** in 70% yield; mp 172–173 °C. IR spectrum (KBr, ν, cm^{-1}): 3186 (NH), 2217 (CN); ^1H NMR spectrum ($CDCl_3$, δ ppm):1.28 (t, $J = 3.30$ Hz, 6H, $3CH_2$), 1.74 (t, $J = 2.34$ Hz, 4H, $2CH_2$), 2.70 (t, $J = 4.50$ Hz, 2H, CH_2), 3.0 (t, $J = 6.30$ Hz, 2H, CH_2), 4.60 (s, 1H, pyrimidine), 6.60–7.30 (m, 9H, Ar-H), 9.6 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 480.2 (M^+, 23). Analysis for $C_{25}H_{25}ClN_4S_2$ (481.08) required: C, 62.42; H, 5.24; N, 11.65; S, 13.33; found: C, 62.50; H, 5.28; N, 11.60; S, 13.13.

[7-(4-Chloro-phenyl)-3-phenyl-2,3,6,7-tetrahydro-cyclohexane (1′-2)thiazolo[4,5-d]pyrimidin-5-yl]-hydrazine (11)

A mixture of compound **4** (1.67 g, 2.5 mmol) and hydrazine hydrate 99% (20 mL) was refluxed for 8 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **11** in 65% yield; mp 167–168 °C. IR spectrum (KBr, ν, cm^{-1}): 3310–3313 (NH_2), 3156, 3170 (NH); ^1H NMR spectrum ($CDCl_3$, δ ppm): 1.28 (t, $J = 3.24$ Hz, 6H, $3CH_2$), 1.76 (t, $J = 2.34$ Hz, 4H, $2CH_2$), 4.2 (s, 2H, NH_2, D_2O exchangeable), 4.70 (s, 1H, pyrimidine), 5.6 (s, 1H, NH, D_2O exchangeable), 6.40–7.20 (m, 9H, Ar-H), 9.6 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 425.24 (M^+, 24). Analysis for $C_{22}H_{24}ClN_5S$ (425.98) required: C, 62.03; H, 5.68; N, 16.44; S, 7.53; found: C, 62.25; H, 5.70; N, 16.25; S, 7.45.

6-(4-Chloro-benzylidene)-9-(4-chloro-phenyl)-3-phenyl-3,9-dihydro-cyclohexane(1′-2)bisthiazolo[3,2-a;4′,5′-d]pyrimidin-7-one (12)

A mixture of compound **9** (1.17 g, 2.5 mmol) and 4-chlorobenzaldehyde (0.35 g, 2.5 mmol) was refluxed in a mixture of glacial acetic acid/acetic anhydride (3:1) containing anhydrous sodium acetate (0.18 g, 2.5 mmol) for 3 h. The reaction mixture was cooled and poured gradually with stirring into cool water (100 mL). The formed solid was filtered off, dried, and recrystallized from dioxane to give **12** in 70% yield; mp 206–207 °C. IR spectrum (KBr, ν, cm^{-1}): 1693 (CO); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.29 (t, $J = 3.28$ Hz, 6H, $3CH_2$), 1.78 (t, $J = 2.34$ Hz, 4H, $2CH_2$), 5.6 (s, 1H, pyrimidine), 6.50–7.30 (m, 14H, Ar-H+methylene H); MS, m/z

(%): 589.1 (M^+, Cl^{35}, 29), 591 (M^+, Cl^{37}, 25). Analysis for $C_{31}H_{25}Cl_2N_3OS_2$ (590.59) required: C, 63.04; H, 4.27; N, 7.11; S, 10.86; found: C, 62.98; H, 4.22; N, 7.00; S, 10.76.

9-(4-Chloro-phenyl)-6-(2,3,4,5,6-pentahydroxy-hexylidene)-3-phenyl-3,9-dihydro-cyclohexane(1′-2)bisthiazolo[3,2-a;4′,5′-d]pyrimidin-7-one (13)

Compound **9** (1.17 g, 2.5 mmol) in dioxane (25 mL) containing a few drops of acetic acid was stirring into a solution of glucose (0.83 g, 2.5 mmol) in water (0.5 ml) at 60 °C for 4 h. The product that separated out on cooling was filtered off, washed with water followed by ethanol, and then dried to give compound **13** in 55% yield; mp 170–171 °C. IR spectrum (KBr, ν, cm^{-1}): 3380–3400 (OH), 1705 (CO); ^1H NMR spectrum ($CDCl_3$, δ ppm): 1.28 (t, $J = 3.40$ Hz, 6H, $3CH_2$), 1.76 (t, $J = 2.40$ Hz, 4H, $2CH_2$), 3.32–3.98 (m, 6H, CH of glucose), 4.7 (m, 5H, OH, D_2O exchangeable), 5.5 (d, $J = 1.66$ Hz, 1H, methylene H), 5.6 (s, 1H, pyrimidine), 6.50–7.20 (m, 9H, Ar–H). Analysis for $C_{30}H_{32}ClN_3O_6S_2$ (630.18) required: C, 57.18; H, 5.12; N, 6.67; S, 10.18; found: C, 57.00; H, 5.15; N, 6.72; S, 10.23.

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