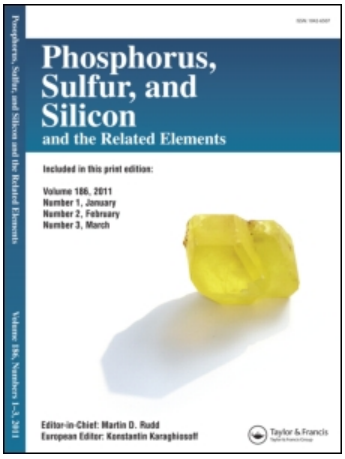

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SYNTHESIS OF SOME NEW 4-AMINO-1,2,4-TRIAZOLE DERIVATIVES AS POTENTIAL ANTI-HIV AND ANTI-HBV

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SYNTHESIS OF SOME NEW 4-AMINO-1,2,4-TRIAZOLE DERIVATIVES AS POTENTIAL ANTI-HIV AND ANTI-HBV

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*Some novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolylisoindole-1,3-dione* ***2a–c*** *were prepared by heating 4-amino-5-aryl-1,2,4-triazole-3-thiones* ***1a–c*** *with different (1,3-dioxo-1,3-dihydro-isoindol-2-yl) carboxylic acids in* $POCl_3$*. Compounds* ***2a***,***b*** *were hydrolyzed using HCl to yield [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolyl-alkylamines* ***3a***,***b****. Coupling* ***1a***,***c*** *with 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide (ABG) afforded the corresponding S-glucosides* ***4a***,***b****, which on oxidation with* $KMnO_4$ *gave the corresponding sulfone* ***5****. Treatment* ***1b***,***c*** *with diphenyl diazomethane afforded benzhydrylsulfanyltriazolylamines* ***7a***,***b****. 1,8-Bis-(4-chloro-phenyl)-bis[1,2,4]triazolo[3,4-*c*-,4′,3′-e][1,2,4,5]dithiadiazine* ***8*** *was formed by oxidation of* ***1b*** *with lead tetracetate. Compound* ***1c*** *reacted with morpholine in the presence of KI and* I_2 *to give the triazolodisulfide* ***9****.*

Keywords: 1,2,4-Triazoles; (1,3-dioxo-1,3-dihydroisoindol-2-yl)carboxylic acids; diphenyldiazomethane; HBV; HIV

INTRODUCTION

Triazoles and their condensed systems have found considerable use in the photographic industry[1] and were reported to possess significant antifungal and antibacterial properties.[2,3] They also showed strong

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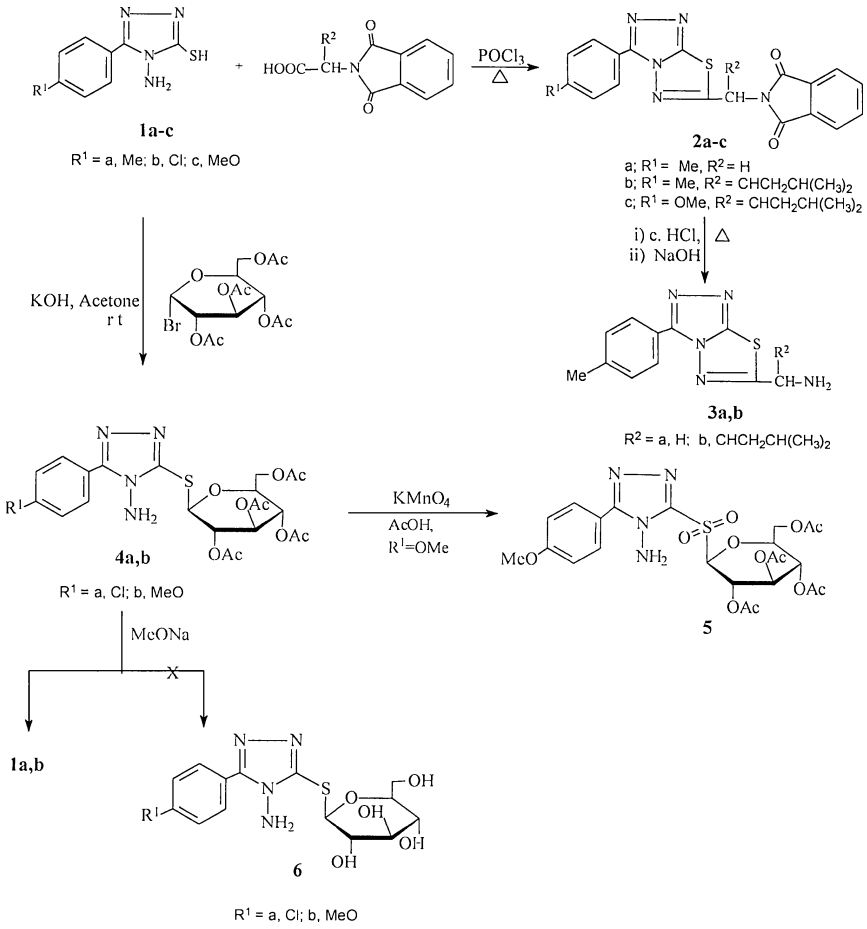
CNS depressant[4] and mild-to-moderate antiinflammatory, hypocholesteremic, and hypertensive activities.[5,6] Triazoles also inhibited the HIV replication in vitro based on nonnucleoside reverse transcriptase inhibitors of action.[7] In addition, they act as antimicrobial and antibacterial agents. These results prompted us to continue our earlier work[8–10] of synthesizing some other new derivatives for evaluating their biological activity as anti-HIV and anti-HBV drugs.

RESULTS AND DISCUSSION

Heating compounds **1a–c** with (1,3-dioxo-1,3-dihydroisoindol-2-yl)-4-methyl-pentanoic acid and/or acetic acid (prepared according to Okuda et al.[11]) in $POCl_3$ at 80°C gave 2-(3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylalkyl)isoindol-1,3-diones (**2a–c**). Hydrolysis of compounds **2a**,**b** with hydrochloric acid afforded 3-methyl-1-(3-*p*-tolyl-[1,2,4]triazolo[3,4-*b*]thiadiazol-6-ylalkyl amines (**3a**,**b**).[12] IR spectra of **2a–c** showed the existence of two carbonyl groups in the range of 1718–1778 cm^{-1}, ^1H NMR spectra showed the presence of a signal at 5.24–5.85 ppm (s, 2H, CH_2), and the ^{13}C NMR spectra showed the existence of C=O at 167.03–168.69 ppm. The structure of compounds **3a**,**b** was confirmed by elemental analysis and different spectroscopic data (IR, ^1H, ^{13}C NMR, and MS). The IR spectra showed the existence of NH_2 in the range of 3307–3391 cm^{-1}, ^1H NMR showed the appearance of NH_2 signal at 3.27 and 2.25 ppm, and ^{13}C NMR showed the absence of C=O signals. Coupling **1b**,**c** with 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide (ABG) in potassium hydroxide solution at room temperature yielded 4-amino-5-aryl-3-(2′,3′,4′,6′)-tetra-*O*-acetyl-β-*D*-glucopyranosyl-thio-1,2,4-triazoles (**4a**,**b**). The structures of compounds **4a**,**b** were confirmed by elemental analyses and different spectroscopic data. Their IR showed sharp bands due to (C=O) at 1752 cm^{-1} and bands due to NH_2 in the range of 3436–3437 cm^{-1}. The ^1H NMR showed the presence of 4 characteristic signals due to four acetyl groups CH_3CO (s) of the sugar moiety in the range of 1.85–2.11 ppm, a doublet due to the anomeric proton at 5.61–5.63 ppm with *J* constants of 10.09 and 10.1 Hz, confirming a β-configuration and a singlet due to NH_2 at 6.02 and 6.10 ppm. MS spectra of compounds **4a**,**b** showed *m*/*z* 556 (M^+, 1.8%) and 552 (M^+, 1%) (Scheme 1). The structure of the *S*-glucoside **4b** was further confirmed by its oxidation with potassium permanganate to afford the corresponding sulfone (**5**). Its IR spectrum showed two bands due to SO_2 at 1040 and 1223 cm^{-1}. Deblocking of **4a**,**b** using sodium methoxide at room temperature yielded the aglycones **1a**,**b** instead of the

desired deblocked 2-[4-amino-5-aryl-4*H*-[1,2,4]triazol-3-ylsulfanyl]-6-hydroxymethyl-tetrahydropy-ran-3,4,5-triol **6** (Scheme 1).

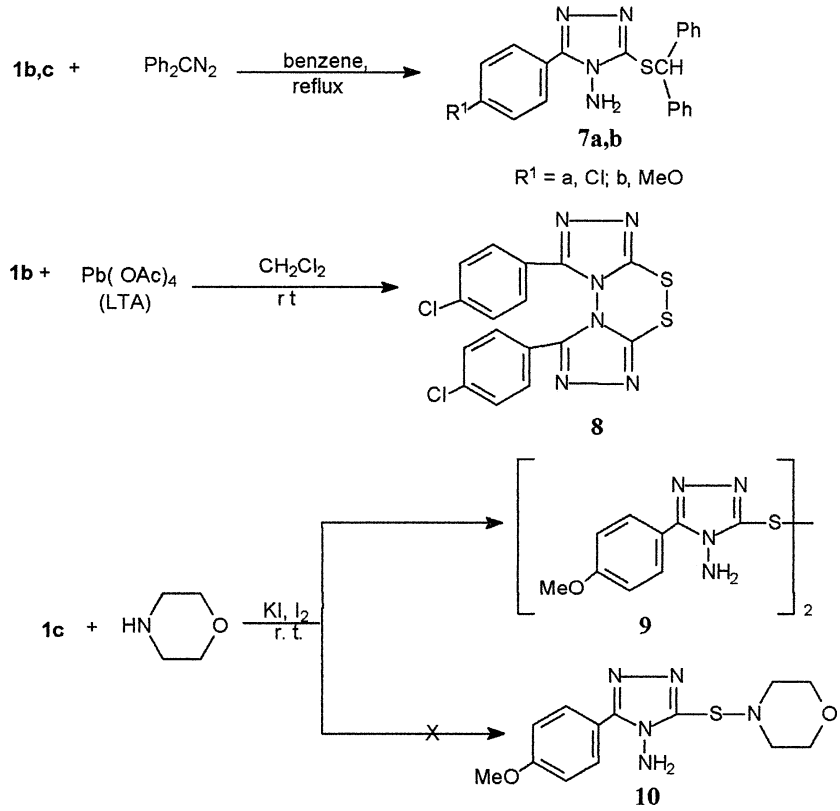


SCHEME 1

Refluxing **1b**,**c** with diphenyl diazomethane (prepared according to Smith and Howard[14]) in anhydrous benzene gave 3-benzhydrylsulfanyl-5-aryl[1,2,4]triazol-4-ylamines (**7a**,**b**). IR spectra showed CH bands in the range of 2924–2936 cm^{-1} and NH_2 bands in the range of 3434–3435 cm^{-1}. ^1H NMR spectra showed a singlet (CH) in the range of 7.16–7.37 ppm, and ^{13}C NMR spectra showed CH signals at 64.16 and 64.13 ppm. Dash et al.[15] reported that oxidation of 4-amino-5-phenyl-1,2,4-triazole-3-thione with lead tetraacetate (LTA) afforded 1,8-bis-phenyl-bis[1,2,4]triazolo[3,4-*C*,4′,3′-*e*][1,2,4,5]dithiadiazine. Similarly,

oxidation of **1b** under the same reaction conditions afforded the corresponding bis-triazolodithidiazine **8**. The ^{1}HNMR and ^{13}CNMR spectra of **8** could not be obtained due to its insolubility in hot DMSO. The IR spectrum of **8** showed the C—Cl band at 742 cm^{-1}, C=N at 1650 cm^{-1}, and CH at 2922 cm^{-1}. The microanalytical data is also in accord with the structure.

Compound **1c** reacted with morpholine in the presence of potassium iodide and iodine at room temperature to afford unexpectedly the disulfide **9** instead of the desired 3-(4-methoxy-phenyl)-5-(morpholin-4-ylsulfanyl)-[1,2,4]triazol-4-ylamine **10**[16] (Scheme 2).



SCHEME 2

BIOLOGICAL ACTIVITY

The test for activity against HIV-1 was performed in MT4 cell cultures infected with either wild-type HIV-1 (strain IIIB) or nonnucleoside

TABLE I IC and CC at 50% Inhibitions Against HBV

Cpd. no.	IC_{50} μM^a	CC_{50} μM^b
3a	35	>100
4a	63	>100
7a	40	>100

[a]50% Inhibitory concentration required to inhibit HBV.
[b]50% Cytotoxic concentration.

reverse transcriptase inhibitors (NNRTIs)-resistant HIV-1 (strain N119) that possessed a substitution of cysteine for tyrosine at position 181 in the reverse transcriptase enzyme (Cys181Tyr mutant strain).

The test for hepatitis B virus (HBV) was performed in the hepatoplastoma cell line HepG2-2.2.15 to evaluate the antiviral effect of the tested compounds against HBV. The cells were incubated in growth medium (RPMI-1640, 10% heat, in activated fetal-calf serum (FCS) and antibiotic) at 37°C, 5% CO_2 with and without test compounds.

All the synthesized new compounds were tested against HIV-1 and HBV. None of the tested compounds showed any significant antiviral activity at 100 μM against HIV-1.

Compounds **3a**, **4a**, and **7a** showed a moderate activity against HBV as shown in Table I. The rest of the tested compounds showed no significant antiviral activity against HBV (Table I).

EXPERIMENTAL

All melting points were uncorrected and performed by the open capillary melting point apparatus. Microanalyses were performed by Microanalytic Unit, Faculty of Science, Cairo University, Egypt. IR spectra were recorded with a Perkin-Elmer spectrometer. The NMR spectra were recorded on a bruker AC 250 FT NMR spectrometer using TMS as an internal standard. Mass spectra (MS) were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer.

Synthesis of 2-(3-Aryl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazol-6-yl)isoindole-1,3-diones (2a–c)

To a solution of **1a**,**c** (0.01 mol) in phosphorus oxychloride (20 ml) was added, in portions, (1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetic acid and/or 4-methylpentanoic acid (0.01 mol). Then the reaction mixture was heated at 80°C for 2 h until the starting materials were consumed (tlc). The reaction mixture was cooled, and sodium hydroxide solution

(1%) was added until a solid product was formed. The solid was filtered off, washed with water, dried, and recrystallized to give **2a–c**.

*2-(3-*p*-Tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylmethyl)isoindole-1,3-dione (2a)*

Yield 2.9 g (80%) [MeOH]; m.p., 240–242°C; IR (KBr): ν (cm^{-1}): 1718 (C=O), 1778 (COMe); ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 5.24 (s, 2H, CH_2), 7.39–8.06 (m, 8H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.97 (CH_3), 37.72 (CH_2), 122.50–140.20 (C_{arom}), 167.03 (CO) ppm; Ms (EI): *m/z* 375 (M^+, 100%). Anal. Calcd. for $C_{19}H_{12}N_5O_2S$: C, 60.95; H, 3.23; N, 18.71. Found: C, 60.92; H, 3.73; N, 18.34.

*2-(3-*p*-Tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylbutyl)-isoindole-1,3-dione (2b)*

Yield 3.5 g (83%) [P.E. 80–100°C]; m.p., 138–140°C; IR (KBr): ν (cm^{-1}) 1718 (C=O); ^{1}H NMR (DMSO-d_6): δ 0.96 (d, 6H, $2CH_3$), 1.63 (m, 1H, HC*H*CH(CH_3)$_2$), 2.17 (m, 1H, *H*CHCH(CH_3)$_2$), 2.34 (s, 3H, CH_3), 2.53 (m, 1H, C*H*(CH_3)$_2$), 5.85 (m, 1H, NC*H*C=N), 7.38 (d, 2H, H_{arom}), 7.49–8.05 (m, 6H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.91 (CH_3), 21.09 (CH_3C*H*CH_3) 22.48 (*C*H_3-Ar), 24.46 (CHCH_2*C*H(CH_3)$_2$), 38.46 (*C*HCH_2CH(CH_3)$_2$), 49.25 (CH*C*H_2CH(CH_3)$_2$), 122.79–140.09 (C_{arom}), 145.18 (C=N) 168.84 (CO) ppm; Ms (EI) *m/z* 431 (M^+, 100%). Anal. Calcd. for $C_{23}H_{21}N_5O_2S$: C, 64.02; H, 4.91; N, 16.23. Found: C, 64.12; H, 4.91; N, 16.74.

*2-(3-*p*-Anisyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-ylbutyl)isoindole-1,3-dione (2c)*

Yield 2.9 g (67%) [MeOH]; m.p., 155–157°C; IR (KBr): ν (cm^{-1}) 1718 (C=O), 1778 (COMe); ^{1}H NMR (DMSO-d_6): δ 0.97 (d, 3H, CH_3),1.00 (d, 3H, CH_3), 1.63 (1H, HC*H*CH(CH_3)$_2$), 2.17 (1H, *H*CHCH(CH_3)$_2$), 2.53 (m, 1H, CHCH_2C*H*(CH_3)$_2$), 3.57 (s, 3H, CH_3O), 5.85 (m, 1H, C*H*CH_2CH(CH_3)$_2$), 7.15 (d, 2H, H_{arom}), 7.95 (m, 4H, H_{arom}), 8.11 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 21.13 (CH_3C*H*CH_3), 22.51 (*C*H_3CHCH_3), 24.47 (CHCH_2*C*H(CH_3)$_2$), 38.41 (*C*HCH_2CH(CH_3)$_2$), 49.27 (CH*C*H_2CH(CH_3)$_2$), 55.27 (CH_3O), 114.51–134.97 (C_{arom}), 145.05 (C=N) 168.69 (CO) ppm; Ms (EI) *m/z* 447 (M^+, 100%). Anal. Calcd. for $C_{23}H_{21}N_5O_3S$: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.72; H, 4.23; N, 15.30.

Hydrolysis of Compounds 2a,b: Formation of (3-p-Tolyl-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-6-yl)alkyl Amines (3a,b)

A suspension of **2a**,**b** (0.01 mol) in aqueous hydrochloric acid 30% (25 ml) was refluxed for 4 h, the reaction mixture was cooled and filtered, and

the filtrate was neutralized using potassium hydroxide solution (10%). The precipitate formed was filtered off, dried, and recrystallized to give **3a**,**b**.

C-*(3-*p-*Tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazol-6-yl)methylamine (3a)*

Yield 1.2 g (50%) [EtOH]; m.p., 190–192°C; IR (KBr): ν (cm^{-1}) 3372 (NH_2, sym), 3307 (NH_2, antisym);^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 3.27 (s, 2H, NH_2), 4.16 (s, 2H, CH_2), 7.41 (d, 2H, H_{arom}), 8.11 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.92 (CH_3), 41.04 (CH_2), 122.73–179.21 (C_{arom}) ppm. Anal. Calcd. for $C_{11}H_{11}N_5S$: C, 53.86; H, 4.52; N, 28.55. Found: C, 53.74; H, 4.43; N, 28.21.

*3-Methyl-1-(3-*p-*tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)butylamine (3b)*

Yield 1.7 g (58%) [MeOH]; m.p., 98–100°C; IR (KBr): ν (cm^{-1}) 3391 (NH_2, sym), 3326 (NH_2, antisym); ^{1}H NMR (DMSO-d_6): δ 0.97 (d, 3H, CH_3), δ 1.00 (d, 3H, CH_3), 1.70 (m, 2H, CHC*H*$_2$ $CH(CH_3)_2$), 1.90 (m, 1H, $CHCH_2CH(CH_3)_2$), 2.42 (s, 3H, C*H*$_3$-Ar), 2.75 (s, 2H, NH_2), 4.26 (m, 1H, C*H*$CH_2CH(CH_3)_2$), 7.42 (d, 2H, H_{arom}), 8.12 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.93 (CH*C*H_3), 21.45 (CH_3CHCH_3), 22.89 (*C*H_3-Ar), 23.81 (*C*$H_2CH(CH_3)_2$), 45.63 (*C*$HCH_2CH(CH_3)_2$), 50.06 (*C*$H(CH_3)_2$), 122.79–182.24 (C_{arom}) ppm; Ms (EI): *m/z* 301 (M^+, 100%). Anal. Calcd. for $C_{15}H_{19}N_5S$: C, 59.77; H, 6.35; N, 23.23. Found: C, 59.52; H, 6.13; N, 23.02. Hrms. Calcd. 301, 1361; Found, 301.17431.

Preparation of 4-Amino-5-aryl-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-thio-1,2,4-triazoles (4a,b)

To a solution of potassium hydroxide (0.56 g, 0.01 mol) in water (5 ml), compounds **1b** and/or **1c** (0.01 mol) were added, and a solution of ABG (4.5 g, 0.011 mol) in acetone (30 ml) was added dropwise, and the reaction mixture was stirred at room temperature for 2 h until the starting material was consumed (tlc). The reaction mixture poured into a cooled water and the solid formed was filtered off, washed with water, dried, and recrystallized from ethanol afforded **4a**,**b**.

*4-Amino-5-p-chlorophenyl-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-*D*-glucopyranosyl)thio-1,2,4-triazole (4a)*

Yield 4.3 g (78%); m.p., 160–162°C; IR (KBr): ν (cm^{-1}) 1752 (CO), 3436 (NH_2, sym), 3375 (NH_2, antisym); ^{1}H NMR (DMSO-d_6): δ 1.85, 1.91, 2.0, 2.11 (4s, 12H, $4CH_3CO$), 4.08 (s, 2H, C6′H2), 4.12 (m, 1H, C'_4H), 5.00 (m, 1H, C'_2H), 5.40 (t, 1H, C′3H), 5.61 (d, 1H,

$J = 10.09$ Hz, $H'_1H_{anomeric}$), 6.13 (s, 2H, NH_2), 7.62 (d, 2H, H_{arom}), 8.11 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.19 (CH_3, C′6), 20.25 (CH_3, C′4) 20.28 (CH_3, C′2) 20.34 (CH_3, C′3), 61.64, 67.59, 69.79, 72.74, 74.61, and 82.37 (C′6, C′4, C′2, C′3, C′5, and $C'_{1anomeric,\ respectively}$), 125.52–134.65 ($C_{arom}$), 149.04(C1=N), 153.29, (C2=N), 169.07, 169.17, 169.42, 169.87 (4CO) ppm; Ms (EI): *m/z* 556 (M^+, 1.8%), 177 (100%). Anal. Calcd. for $C_{22}H_{25}ClN_4O_9S$: C, 47.44; H, 4.52; N, 10.06. Found: C, 47.35; H, 4.63; N, 9.91. Hrms: Found: 555.9850, Calcd. 556.1030.

*4-Amino-5-*p*-anisyl-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-thio)-1,2,4-triazole (4b)*

Yield 4.1 g (85%); m.p., 80–82°C; IR (KBr): ν (cm^{-1}) 1752 (CO), 3437 (NH_2, sym), 3375 (NH_2, antisym); ^1H NMR (DMSO-d_6): δ 1.85, 1.91, 2.0, 2.11 (4s, 12H, $4CH_3CO$), 4.08 (s, 2H, C'_6H2), 4.15 (m, 1H, C'_4H), 5.00 (m, 1H, C'_2H), 5.31 (t, 1H, C′3H), 5.63 (d, 1H, $J = 10.1$ Hz, $H1'H_{anomeric}$), 6.02 (s, 2H, NH_2), 7.08 (d, 2H, H_{arom}), 8.01 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.20 (CH_3, C′6), 20.25 (CH_3, C′4) 20.29 (CH_3, C′$_2$) 20.35 (CH_3, C′3), 61.66, 67.64, 69.81, 72.74, 74.59, and 82.52 (C′6, C′4, C′2, C′3, C′5 & $C'1_{anomeric}$), 113.83–129.36 (C_{arom}), 148.104 (C_1=N) 154.09 (C_2=N), 169.08, 169.19, 169.43, and 169.90 (4CO) ppm; Ms (EI): *m/z* 552 (M^+, 1%), 43 (100%). Anal. Calcd. for $C_{23}H_{28}N_4O_{10}S$: C, 50.00; H, 5.11; N, 10.14. Found: C, 49.91; H, 5.21; N, 10.13.

4-Amino-5-p-anisyl-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl-sulfonyl)-1,2,4-triazole (5)

To a solution of **4b** (1.1 g, 0.002 mol) in glacial acetic acid (25 ml) was added gradually with stirring a solution of potassium permanganate (0.06 g, 0.004 mol) in water (10 ml) for 30 min. Stirring was continued for 5 h at room temperature, and the mixture was then poured into crushed ice. The solid formed was collected and recrystallized from ethanol to afford **5**. Yield 3.1 g (54%); m.p., 60–62°C; IR (KBr): ν (cm^{-1}) 1040, 1223 (SO_2) 1749 (C=O), 3426 (NH_2, sym), 3375 (NH_2, antisym); ^1H NMR (DMSO-d_6): δ 1.85, 1.91, 2.03, 2.16 (4s, 12H, $4CH_3CO$), 4.08 (s, 2H, C'_6H2), 4.12 (m, 1H, C'_4H), 5.00 (m, 1H, C'_2H), 5.32 (t, 1H, C'_3H), 5.6 (d, 1H, $J = 10.1$ Hz, $C'_1H_{anomeric}$), 6.02 (s, 2H, NH_2), 7.08 (d, 2H, H_{arom}), 8.01 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 20.20, 20.25, 20.29, and 20.35 ($4CH_3$), 61.66, 67.64, 69.81, 72.74, 74.59, and 82.52 (C′6, C′4, C′2, C′3, C′5, and $C'1_{anomeric}$), 113.83–129.36 (C_{arom}), 148.10 (C1=N), 154.09 (C2=N), 169.08, 169.19, 169.43, and 169.90 (4CO) ppm. Anal. Calcd. for $C_{23}H_{28}N_4O_{12}S$: C, 47.26; H, 4.83; N, 9.58. Found: C, 47.0; H, 4.29; N, 9.41.

Deblocking of 4a,b

Each of Compounds **4a**,**b** (0.01 mol) was dissolved in 35 ml methanol, and two drops of 0.01 N sodium methoxide solution were added. The reaction mixture was left at 20°C for 5 h until the starting material was consumed (tlc). The solvent was evaporated in vacuum, and the residual solid was dissolved in water neutralized with dill HCl. The solid formed was filtered off, washed with water, dried, and recrystallized from ethanol to give the starting materials **1a**,**b**. **1a** Yield 60%; m.p., 205–207°C. **1b** Yield 76%; m.p., 211–213°C. (Their mixed melting points with authentic samples of **1a** and **1b** give no depression).

Synthesis of 3-Benzhydrylsalfanyl-5-aryl-[1,2,4]triazol-4-ylamines (7a,b)

A solution of diphenyl diazomethane (1.95 g, 0.01 mol) in anhydrous benzene (20 ml) was added to a suspension of **1b** and/or **1c** (0.01 mol) in anhydrous benzene (30 ml). The reaction mixture was heated on a water bath for 8 h until the starting material was consumed (tlc). The solvent was evaporated under vacuum, and diethyl ether (30 ml) was added to the residual oil. The solid formed was filtered off, dried, and chromatographed on the column of a silica gel (P.E./ EtOAc; 10:1, v/v) to give **7a**,**b**.

3-Benzhydrylsalfanyl-5-(4-chlorophenyl)-[1,2,4]triazol-4ylamine (7a)

Yield 2.4 g (60%); m.p., 175–177°C; IR (KBr): ν (cm^{-1}) 3434 (NH_2, antisym), 3296 (NH_2, sym); ^1H NMR (DMSO-d_6): δ 5.94 (s, 2H, NH_2), 7.37 (m, 11H, C*H*Ph_2), 7.61 (d, 2H, H_{arom}), 8.04 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 64.16 (CH), 123.96–167.79 (C_{arom}) ppm. Ms (EI): *m/z* 392 (M^+, 8%), 167 (100%). Anal. Calcd. for $C_{21}H_{17}ClN_4S$: C, 64.20; H, 4.36; N, 14.26. Found: C, 64.41; H, 4.34; N, 14.05.

3-Benzhydrylsalfanyl-5-(4-anisyl)-[1,2,4]triazol-4-ylamine (7b)

Yield 2.8 g (74%); m.p., 90–92°C; IR (KBr): ν (cm^{-1}) 3435 (NH_2, antisym), 3027 (NH_2, sym); ^1H NMR (DMSO-d_6): δ 3.83 (s, 3H, CH_3O) 6.92 (d, 2H, H_{arom}), 7.16 (s, 1H, CH), 7.21–7.36 (m, 10H, 2Ph) 8.10 (d, 2H, H_{arom}); ^{13}C NMR (DMSO-d_6): 55.23 CH_3O 64.13 (CH), 123.96–167.79 (C_{arom}) ppm. Anal. Calcd. for $C_{22}H_{20}N_4OS$: C, 68.0; H, 5.19; N, 14.42. Found: C, 68.22; H, 5.17; N, 14.33.

1,8-Bis-(4-chloro-phenyl)-bis[1,2,4]triazolo[3,4-c,4′,3′-e]-[1,2,4,5]dithiadiazine (8)

To a stirred solution of **1b** (2.26 g, 0.01 mol) in anhydrous methylene chloride (60 ml), lead tetraacetate (6.66 g, 0.015 mol) was added in portions during 15 min. The reaction mixture was stirred for 2 h at room temperature until the starting material was consumed (tlc). Then lead salts was filtered off and washed with methylene chloride (20 ml). The two filtrates were concentrated to give pink crystals that were dried and recrystallized from DMF to give **8**. Yield 3.7 g (89%); m.p., >320°C; IR (KBr): ν (cm^{-1}) 742 (C—Cl), 1650 (C=N) and 2922 (CH). Anal. Calcd. for $C_{16}H_8Cl_2N_6S_2$: C, 45.83; H, 1.92; N, 20.04. Found: C, 45.72; H, 2.01; N, 20.14.

4-Amino-5-(p-methoxyphenyl)-1,2,4-triazole-3-disulfide (9)

To a solution of **1c** (1.3 g, 0.006 mol) in distilled water (10 ml) was added a mixture of sodium hydroxide solution (0.27 g, 0.012 mol) in water (10 ml) and morpholine (0.87 g, 0.01 mol). The reaction volume was increased to 25 ml with distilled water until a clear solution was obtained. A solution of iodine (1.53 g, 0.006 mol) and potassium iodide (3.3 g, 0.006 mol) in distilled water (20 ml) was added dropwise to the above reaction mixture. The reaction mixture was stirred for 1 h until the starting material was consumed (tlc). The solid product was filtered off, dried, and recrystallized from MeOH/H_2O to afford **9**. Yield 2.3 g (59%); m.p., 165–167°C; IR (KBr): ν (cm^{-1}) 2982 (NH_2, sym), 2842 (NH_2, antisym); ^{1}H NMR (DMSO-d_6): δ 5.98 (s, 4H, $2NH_2$), 7.13 (d, 2H, H_{arom}), 7.97 (d, 2H, H_{arom}) ppm;^{13}C NMR (DMSO-d_6): 55.35 (CH_3O), 113.72–131.27 (C_{arom}), 166.72 ($COCH_3$) ppm; Ms (EI) *m/z* 292 ($C_{10}H_{10}N_7S_2$, 40%), 222 (M^+, 87%), 175 (100%). Anal. Calcd. for $C_{18}H_{18}N_8O_2S_2$: C, 48.86; H, 4.10; N, 25.32. Found: C, 48.91; H, 4.23; N, 25.24.

VIRUSES AND CELLS

The HIV-1 strains HTLV-IIIB[17] and the NNRTI resistant strain N119[18] were propagated in H9 cells[19] at 37°C, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquotted, and stored at −80°C until use. Both HIV-1 strains were obtained from the NIH AIDS Research and Reference Program.

Compounds were examined for possible antiviral activity against both strains of HIV-1 using MT4 cells as target cells. MT4 cells were

incubated with virus (0.005 MOI) and growth medium containing the test dilutions of compound for six days in parallel with virus-infected and uninfected control cultures without compound added. Expression of HIV in the cultures was indirectly quantified using the MTT assay. Compounds mediating less than 30% reduction of HIV expression were considered without biological activity. Compounds were tested in parallel for cytotoxic effect in uninfected MT4 cultures containing the test dilutions of compound as described above. A 30% inhibition of cell growth relative to control cultures was considered significant.

The average production HBV virion DNA from cell cultures with the addition of different concentrations of the tested compounds was expressed relative to the HBV virion DNA in the culture supernatant without the antiviral compound. Quantitation of HBV-DNA was done using a semiquantitative PCR followed by DIG PCR ELISA as previously described.[20]

The 50% inhibitory concentration (IC_{50}) and the 50% cytotoxic concentration (CC_{50}) were determined by interpolation from the plots of percent inhibition versus concentration of compound.[21]

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