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Synthesis and Antiviral Evaluation against cytomegalovirus (CMV) and Varicella-zoster virus (VZV) in human embryonic lung (HEL) cells of thiadiazol and thioazolidinone derivatives

Nasir Hussain^{*1}, Saba Khan¹, Maqbool Ahmed², Ajit Joshi³, Mohammad Ashid³ and Prabhunath Yogi³

¹Synthetic organic chemistry lab. Vidya Bhawan Rural Institute Udaipur India

²Head-R&D, Lanxess india Private Limited, GIDC, Jhagadia Industrial Estate, Bharuch, Gujrat India 393110

³Synthetic organic chemistry lab. Mewar University, chittorgarh India

E-mail: nasirchem786@gmail.com

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Abstract: In our present study a series of thiazolidine and thiazolidinone based heterocyclic entities (5a-e, 6a-e) were designed, synthesized and evaluated for their antiviral activity. The chemical structures of the new synthesized compounds were characterized by FTIR, ¹HNMR, ¹³CNMR, MS spectroscopy and Elemental analyses. Compounds 5a-e and 6a-e were screened against cytomegalovirus (CMV) [strains AD-169 and Davis], varicella-zoster virus (VZV) [TK+ VZV strain OKA, and TK– VZV strain 07/1] in human embryonic lung (HEL) cells. The minimum inhibitory concentration (MIC) and the minimal cytotoxic concentration (MCC) or the cytotoxic concentration required to reduce cell growth by 50 % (CC₅₀), were obtained. (S)-9-(2,3-dihydroxypropyl)adenine [(S)-DHPA], ribavirin, acyclovir, cidofovir and ganciclovir were used as the reference compounds. Many of synthesized compounds show good antiviral activity.

Keywords: o-Phenyldiamine, Substituted aldehydes, Bromoethoxyphthalimide, Cytomegalovirus (CMV) and Varicella-zoster virus (VZV).

Introduction

Thiazolidine derivatives are reported to show a variety of biological activities. Depending on the substituent's, this heterocycle can induce different pharmacological properties such as antibacterial, antifungal (1), antidiabetic (2,3), cardiotonic (4), anticonvulsant (5), antiinflammatory activity (6). Thiazoles

and their derivatives have been reported to possess antibacterial (7) and antifungal (8) activities. It has been established that the introduction of arylidene moieties at different positions of the thiazolidine ring enhanced antimicrobial activity (9). In the present study, in view of the antimicrobial property of the above pharmacophores, some novel thiazole derivatives that contain thiazolidinedione

moiety were synthesized. Thiazolidines have reported as novel inhibitors of the bacterial enzyme Mur B that was a precursor acting during the biosynthesis of peptidoglycan (10). Furthermore, antibacterial (11), antifungal (12), hypoglycemic activity (13), carbonic anhydrase inhibitory (14), anti-inflammatory (15) and antitumor (16), properties of sulfamoyl moiety were described. Benzimidazole derivatives possess diverse pharmacological activities, including antimicrobial (17,19), antiviral (20), antineoplastic (21), analgesic(22), anti-inflammatory (23-24), antihypertensive (25) and vasodilating activities (26).

Material and method

General

Melting points were taken in open capillary tubes and therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spots was carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm^{-1} ranges using KBr discs on FTIR Perkin Elmer spectrometers and ^1H NMR were recorded on a Bruker DRX-300 MHz spectrometer (DMSO) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Structure of all the synthesized compounds was assigned on basis of their analytical Data and spectral data.

Chemistry & synthesis

General procedure for synthesis of N,N'-bis[(substitutedphenyl)methylidene]benzene-1,4-diamine (2a-e)

A mixture of compound (1a-e) (.02 mole), p-phenyldiamine (.01mole) were dissolved in methanol (30 ml) and refluxed for 6 hrs. The mixture was cooled, solid was filtered, dried

and recrystallized from ethanol.

N,N'-bis[(phenyl)methylidene]benzene-1,4-diamine (2a).

IR (KBr) cm^{-1} : 3073 (C-H str., Ar-H), 1585 (C=N str.), 1482 (C=C); ^1H NMR (DMSO) δ : 7.13-6.85 (m, 14H, Ar-H), 5.39 (s, 2H, =CH-Ar); ^{13}C -NMR (CDCl_3) δ : 122.6, 126.43, 129.21, 133.52, 137.80, 148.20, 154.39; MS : (m/z) $[\text{M}]^+$ 284.

N,N'-bis[(4-chlorophenyl)methylidene]benzene-1,4-diamine (2b).

IR (KBr) cm^{-1} : 3080 (C-H str., Ar-H), 1588 (C=N str.), 1496 (C=C), C-Cl (780); ^1H NMR (DMSO) δ : 7.46-6.98 (m, 12H, Ar-H), 5.45 (s, 2H, =CH-Ar); ^{13}C -NMR (CDCl_3) δ : 123.3, 127.10, 131.50, 135.16, 137.86, 148.20, 154.39; MS : (m/z) $[\text{M}]^+$ 354.

N,N'-bis[(4-methoxyphenyl)methylidene]benzene-1,4-diamine (2c).

IR (KBr) cm^{-1} : 3082 (C-H str., Ar-H), 1576 (C=N str.), 1485 (C=C), 1215 (C-O-C); ^1H NMR (DMSO) δ : 7.52-6.93 (m, 12H, Ar-H), 5.56 (s, 2H, =CH-Ar), 3.54 (s, 6H, OCH_3); ^{13}C -NMR (CDCl_3) δ : 55.8, 118.6, 124.5, 128.72, 131.32, 146.60, 158.28, 162.52; MS : (m/z) $[\text{M}]^+$ 344.

N,N'-bis[(3-nitrophenyl)methylidene]benzene-1,4-diamine (2d).

IR (KBr) cm^{-1} : 3090 (C-H str., Ar-H), 1593 (C=N str.), 1482 (C=C), 1512-1356 (NO_2); ^1H NMR (DMSO) δ : 7.52-6.93 (m, 12H, Ar-H), 5.56 (s, 2H, =CH-Ar); ^{13}C -NMR (CDCl_3) δ : 125.6, 128.10, 128.80, 129.70, 134.26, 138.10, 148.20, 149.30, 159.39; MS : (m/z) $[\text{M}]^+$ 374.

N,N'-bis[(4-N,Ndimethylaminephenyl)methylidene]benzene-1,4-diamine (2e).

IR (KBr) cm^{-1} : 3083 (C-H str., Ar-H), 1589

(C=N str.), 1450 (C=C); ^1H NMR (DMSO) δ : 7.48-6.90 (m, 12H, Ar-H), 5.48 (s, 2H, =CH-Ar), 3.12 {s, 6H, N(CH₃)₂}; ^{13}C -NMR (CDCl₃) δ : 42.1, 128.3, 125.6, 128.75, 128.80, 148.20, 155.33, 159.39; MS : (m/z) [M]⁺ 370.

General procedure for synthesis of 2,2'-[benzene-1,4-diylbis{2-(substituted phenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}]diacetic acid (3a-e).

A mixture of equimolar amounts of (2a-e) (0.01 mole) and mercaptosuccinic acid (0.01 mole) in ethanol (40 ml) with a pinch of anhydrous ZnCl₂ was refluxed for 12-14 hrs. on a water bath. The reaction mixture was left to cool at room temperature. The solid product so formed was collected and crystallized from methanol to afford (3a-e).

2,2'-[benzene-1,4-diylbis{2-(phenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}]diacetic acid (3a).

IR (KBr) cm⁻¹: 3080 (C-H str., Ar-H), 2705 (str., COOH), 1736 (str., C=O acid), 1710 (str., C=O); ^1H NMR (DMSO) δ : 10.5 (s, 2H, COOH), 7.34-6.92 (m, 14H, Ar-H), 4.92 (s, 2H = CH-Ar), 3.7 (*J* = 6.3 Hz, t, 2H, CH), 3.3 (*J* = 13.5 Hz, dd, 2H, CH_a distereotropic proton), 3.1 (*J* = 13.5 Hz, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl₃) δ : 39.3, 48.3, 62.1, 126.5, 128.5, 130.3, 132.4, 137.5, 140.3, 162.5, 167.3; MS : (m/z) 548.

2,2'-[benzene-1,4-diylbis{2-(4-chlorophenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}]diacetic acid (3b)

IR (KBr) cm⁻¹: 3088 (C-H str., Ar-H), 2732 (str., COOH), 1735 (str., C=O acid), 1715 (str., C=O), 786 (C-Cl); ^1H NMR (DMSO) δ : 10.8 (s, 2H, COOH), 7.43-6.97 (m, 12H, Ar-H), 4.94 (s, 2H = CH-Ar), 3.9 (*J* = 6.3 Hz, t, 2H, CH), 3.5 (*J* = 13.2 Hz, dd, 2H, CH_a distereotropic proton), 3.3 (*J* = 13.2 Hz, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl₃) δ : 41.3, 49.2, 69.3, 128.7, 132.5, 132.6, 133.8, 135.9, 139.3, 167.3, 169.4; MS : (m/z) 617.

2,2'-[benzene-1,4-diylbis{2-(4-methoxyphenyl-

4-oxo-1,3-thiazolidine-3,5-diyl)}]di-acetic acid (3c).

IR (KBr) cm⁻¹: 3086 (C-H str., Ar-H), 2719 (str., COOH), 1728 (str., C=O acid), 1718 (str., C=O), 1243 (C-O-C); ^1H NMR (DMSO) δ : 10.6 (s, 2H, COOH), 7.12-6.73 (m, 12H, Ar-H), 4.96 (s, 2H = CH-Ar), 3.8 (*J* = 6.9 Hz, t, 2H, CH), 3.5 (*J* = 13.6 Hz, dd, 2H, CH_a distereotropic proton), 3.3 (*J* = 13.6 Hz, dd, 2H, CH_b distereotropic proton), 3.1 (s, 6H, OCH₃); ^{13}C -NMR (CDCl₃) δ : 37.3, 49.6, 50.6, 69.8, 121.0, 130.5, 132.6, 134.6, 137.5, 157.3, 168.5, 169.7; MS : (m/z) 608.

2,2'-[benzene-1,4-diylbis{2-(4-nitrophenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}]diacetic acid (3d).

IR (KBr) cm⁻¹: 3091 (C-H str., Ar-H), 2739 (str., COOH), 1741 (str., C=O acid), 1719 (str., C=O), 1350-1613 (str. NO₂); ^1H NMR (DMSO) δ : 11.1 (s, 2H, COOH), 7.95-6.81 (m, 12H, Ar-H), 5.07 (s, 2H = CH-Ar), 3.9 (*J* = 6.4 Hz, t, 2H, CH), 3.2 (*J* = 13.8 Hz, dd, 2H, CH_a distereotropic proton), 2.8 (*J* = 13.8 Hz, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl₃) δ : 40.5, 49.6, 74.3, 122.5, 127.3, 128.1, 132.5, 134.3, 139.5, 142.3, 146.5, 167.7, 169.7; MS : (m/z) 638.

2,2'-[benzene-1,4-diylbis{2-(4-N,N-dimethylaminephenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}] diacetic acid (3e).

IR (KBr) cm⁻¹: 3084 (C-H str., Ar-H), 2725 (str., COOH), 1739 (str., C=O acid), 1719 (str., C=O); ^1H NMR (DMSO) δ : 10.1 (s, 2H, COOH), 7.31-6.82 (m, 12H, Ar-H), 4.90 (s, 2H = CH-Ar), 3.7 (*J* = 5.9 Hz, t, 2H, CH), 3.4 (*J* = 13.1 Hz, dd, CH_a distereotropic proton), 3.1 (*J* = 13.1 Hz, dd, CH_b distereotropic proton), 2.85 (s, 6H, N-CH₃); ^{13}C -NMR (CDCl₃) δ : 38.5, 42.3, 49.1, 50.6, 109.5, 126.5, 130.1, 132.1, 133.6, 138.5, 166.3, 168.5; MS: (m/z) 634.

General procedure for Synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-

(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-substitutedphenyl)thioazolidin-3-yl}phenyl]-2-(-4-substitutedphenyl)thioazolidine-4-one (**4a-e**).

A mixture of *o*-phenylenediamine (0.02 mole), Compound (**3a**) (0.01 mole) and polyphosphoric acid (5 ml) was refluxed for 4h. The reaction mixture was then cooled and neutralized with ice-cold. The solid separated out was filtered, washed with water and dried under vacuum to afford an off-white solid. The crude product was recrystallized from hot aq. ethanol to obtain the pure compound.

*Synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-phenylthioazolidin-3-yl}phenyl]-2-phenylthioazolidine-4-one (**4a**).*

IR (KBr) cm^{-1} : 3370 (NH str.), 3021 (C-H str., Ar-H), 1709 (str., C=O), 1519 (str. C=N), 1453 (C=C); ^1H NMR (DMSO) δ : 7.40-6.70 (m, 22H, Ar-H), 6.21 (s, 2H, NH), 5.64 (s, 2H, =CH-Ar), 4.16 ($J = 6.4 \text{ Hz}$, t, 2H, CH), 2.33 ($J = 13.1 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 2.35 ($J = 13.1 \text{ Hz}$, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl_3) δ : 39.3, 48.3, 62.1, 126.5, 128.5, 130.3, 132.4, 137.5, 140.3, 162.5, 167.3; MS : (m/z) 692.

*Synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-chlorophenyl)thioazolidin-3-yl}phenyl]-2-(-4-chlorophenyl)thioazolidine-4-one (**4b**).*

IR (KBr) cm^{-1} : 3384 (NH str.), 3049 (C-H str., Ar-H), 1717 (str., C=O), 1525 (str. C=N), 1450 (C=C), 790 (C-Cl); ^1H NMR (DMSO) δ : 7.42-6.78 (m, 20H Ar-H), 6.25 (s, 2H, NH), 5.69 (s, 2H, CH-Ar), 4.17 ($J = 6.3 \text{ Hz}$, t, 2H, CH), 2.37 ($J = 13.4 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 2.35 ($J = 13.4 \text{ Hz}$, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl_3) δ : 41.3, 49.2, 69.3, 128.7, 132.5, 132.7, 133.8, 135.9, 139.3, 167.3, 169.4; MS:(m/z) 761.

*Synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-methoxyphenyl)thioazolidin-3-yl}phenyl]-2-(-4-methoxyphenyl)thioazolidine-4-one (**4c**).*

IR (KBr) cm^{-1} : 3380 (NH str.), 3041 (C-H str., Ar-H), 1712 (str., C=O), 1521 (str. C=N), 1442 (C=C), 1219 (C-O-C); ^1H NMR (DMSO) δ : 7.44-6.79 (m, 18H Ar-H), 6.30 (s, 1H, NH), 5.73 (s, 1H, CH-Ar), 4.2 ($J = 6.9 \text{ Hz}$, t, CH), 3.1 (s, OCH_3), 2.39 ($J = 12.4 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 2.35 ($J = 12.4 \text{ Hz}$, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl_3) δ : 37.3, 49.6, 50.6, 69.8, 121.3, 130.5, 132.6, 134.6, 137.5, 157.3, 168.5, 169.7; MS : (m/z) 752.

*Synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(3-nitrophenyl)thioazolidin-3-yl}phenyl]-2-(-3-nitrophenyl)-thioazolidine-4-one (**4d**).*

IR (KBr) cm^{-1} : 3387 (NH str.), 3053 (C-H str., Ar-H), 1731 (str., C=O), 1530 (str. C=N), 1459 (C=C), 1475-1350 (NO_2); ^1H NMR (DMSO) δ : 7.52-6.81 (m, 18H Ar-H), 6.35 (s, 1H, NH), 5.75 (s, 1H, CH-Ar), 4.32 ($J = 6.4 \text{ Hz}$, t, 2H, CH), 2.41 ($J = 11.9 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 2.39 ($J = 11.9 \text{ Hz}$, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl_3) δ : 40.5, 49.6, 74.3, 122.5, 127.3, 128.1, 132.5, 134.3, 139.5, 142.3, 146.5, 169.3, 167.7; MS:(m/z) 782.

*Synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-N,N-dimethylaminephenyl)thioazolidin-3-yl}phenyl]-2-(-4-N,N-dimethylaminephenyl)thioazolidine-4-one (**4e**).*

IR (KBr) cm^{-1} : 3382 (NH str.), 3038 (C-H str., Ar-H), 1716 (str., C=O), 1515 (str. C=N), 1441 (C=C); ^1H NMR (DMSO) δ : 7.48-6.79 (m, 20H Ar-H), 6.27 (s, 1H, NH), 5.70 (s, 1H, CH-Ar), 4.12 ($J = 6.2 \text{ Hz}$, t, CH), 3.2 (s, 6H, N-CH_3), 2.38 ($J = 11.2 \text{ Hz}$, 2H, dd, CH_a distereotropic proton), 2.31 (J

=11.2 Hz, dd, 2H, CH_b distereotropic proton); ¹³C-NMR (CDCl₃) δ : 38.5, 42.3, 49.1, 72.3, 109.5, 126.5, 130.1, 132.1, 133.6, 138.3, 166.3, 168.5; MS : (m/z) 778.

General procedure for Synthesis of bis-(N-ethoxyphthalimide)-5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-substitutedphenyl)thioazolidin-3-yl}phenyl]-2-(-4-substitutedphenyl)thioazolidine-4-one(5a-e).

Compound (4a-e) (0.01 mole) and bromoethoxyphthalimide (0.02 mole) were dissolved in absolute ethanol. (2 mL) Pyridine was added as a base and then reaction mixture was refluxed for 6 hr. Residue was recrystallized from methanol.

Synthesis of bis-(N-ethoxyphthalimide)-5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-phenylthioazolidin-3-yl}phenyl]-2-phenylthioazolidine-4-one (5a).

IR (KBr) cm⁻¹: 3021 (C-H str., Ar-H), 2958 (CH₂ str.), 1791 (str., C=O), 1735, 1710 (str., C=O), 1518 (str. C=N), 1458 (C=C), 1128 (N-O str.); ¹H NMR (DMSO) δ : 7.80-7.08 (m, 30H, Ar-H), 5.68 (s, 1H, =CH-Ar), 4.44 (J = 4.7 Hz, t, 4H, O-CH₂), 4.37 (J = 4.7 Hz, t, 4H, N-CH₂), 3.90 (J = 5.5 Hz, t, 2H, CH), 3.22 (J = 12.1 Hz, dd, 2H, CH_a distereotropic proton), 3.12 (J = 12.1 Hz, dd, 2H, CH_b distereotropic proton); ¹³C-NMR (CDCl₃) δ : 39.3, 48.3, 62.1, 126.5, 128.5, 130.3, 132.4, 137.5, 140.3, 162.5, 167.3; MS : (m/z) 1072 [M]⁺, 994[M-C₆H₅]⁺, 847[M-C₁₄H₉NO₂]⁺, 770[M-C₂₀H₁₄NO₂]⁺, 726[M-C₂₂H₁₈NO₃]⁺, 580[M-C₃₀H₂₂N₂O₅]⁺, 540[M-C₃₂H₂₆N₂O₆]⁺, 420 [M-C₃₉H₃₀N₄O₆]⁺, 406[M-C₄₀H₃₃N₄O₆]⁺, 290[M-C₄₇H₃₇N₆O₆]⁺.

Synthesis of bis-(N-ethoxyphthalimide)-5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-

chlorophenyl)thioazolidin-3-yl}phenyl]-2-(-4-chlorophenyl)thioazolidine-4-one (5b).

IR (KBr) cm⁻¹: 3029 (C-H str., Ar-H), 1793 (str., C=O), 1737 (Str., C=O), 1618 (str. C=N), 1454 (C=C), 792 (C-Cl); ¹H NMR (DMSO) δ : 7.85-7.12 (m, 28H, Ar-H), 5.71 (s, 2H, CH-Ar), 4.45 (J = 3.9 Hz, t, 4H, O-CH₂), 4.35 (J = 5.7 Hz, t, 1H, CH), 3.92 (J = 3.9 Hz, t, 4H, N-CH₂), 3.24 (J = 12.4 Hz, dd, 2H, CH_a distereotropic proton), 3.17 (J = 12.4 Hz, dd, 2H, CH_b distereotropic proton); ¹³C-NMR (CDCl₃) δ : 172.44, 165.12, 154.21, 145.23, 143.89, 138.42, 135.02, 133.24, 132.56, 131.04, 130.23, 128.92, 126.72, 124.70, 79.05, 68.28, 46.10, 40.21; MS: (m/z) 1140 [M]⁺, 1142 [M+2]⁺, 1144 [M+4]⁺, 1028 [M-C₆H₄Cl]⁺, 916 [M-C₁₂H₈Cl₂]⁺, 770 [M-C₂₀H₁₂Cl₂NO₂]⁺, 726 [M-C₂₂H₁₆Cl₂NO₃]⁺, 580 [M-C₃₀H₂₀Cl₂N₂O₅]⁺, 536 [M-C₃₂H₂₂Cl₂N₂O₆]⁺, 420 [M-C₃₉H₂₄Cl₂N₄O₆]⁺, 304 [M-C₄₆H₃₀Cl₂N₆O₆]⁺.

Synthesis of bis-(N-ethoxyphthalimide)-5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-methoxyphenyl)thioazolidin-3-yl}phenyl]-2-(-4-methoxyphenyl)thioazolidine-4-one (5c).

IR (KBr) cm⁻¹: 3025 (C-H str., Ar-H), 1790 (str., C=O), 1733 (Str., C=O), 1613 (str. C=N), 1458 (C=C), 1223 (C-O-C); ¹H NMR (DMSO) δ : 7.82-7.11 (m, 28H, Ar-H), 5.70 (s, 2H, CH-Ar), 4.47 (J = 3.2 Hz, t, 4H, O-CH₂), 4.32 (J = 5.4 Hz, t, 2H, CH), 3.91 (J = 3.2 Hz, t, 4H, N-CH₂), 3.42 (s, 6H, OCH₃), 3.12 (J = 11.7 Hz, dd, 2H, CH_a distereotropic proton), 3.10 (J = 11.7 Hz, dd, 2H, CH_b distereotropic proton); ¹³C-NMR (CDCl₃) δ : 170.12, 163.78, 152.21, 150.34, 142.29, 139.74, 138.42, 136.57, 135.65, 134.72, 133.55, 131.21, 129.43, 127.92, 122.34, 77.09, 72.32, 49.31, 42.65; MS : (m/z) 1130 [M]⁺, 1024 [M-C₇H₆O]⁺, 916 [M-C₁₄H₁₄O₂]⁺, 770 [M-C₂₂H₁₈NO₄]⁺, 726 [M-C₂₄H₂₂NO₅]⁺, 580 [M-C₃₂H₂₆N₂O₇]⁺, 536 [M-C₃₄H₃₀N₂O₈]⁺, 420 [M-C₄₁H₃₄N₄O₈]⁺.

Synthesis of bis-(N-ethoxyphthalimide)-5-[(1H-

benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-methoxyphenyl)thioazolidin-3-yl}phenyl]-2-(4-nitrophenyl)thioazolidine-4-one (5d).

IR (KBr) cm^{-1} : 3055 (C-H str., Ar-H), 1796 (str., C=O), 1739 (Str., C=O), 1621 (str. C=N), 1460 (C=C), 1498-1362 (NO_2 , str.); ^1H NMR (DMSO) δ : 7.92-7.14 (m, 28H, Ar-H), 5.74 (s, 2H, CH-Ar), 4.51 ($J = 3.3 \text{ Hz}$, t, 4H, O- CH_2), 4.28 ($J = 5.8 \text{ Hz}$, t, 2H, CH), 3.95 ($J = 3.3 \text{ Hz}$, t, 4H, N- CH_2), 3.16 ($J = 11.9 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 3.12, ($J = 11.9 \text{ Hz}$, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl_3) δ : 173.21, 168.02, 153.72, 150.74, 146.08, 144.91, 142.35, 139.50, 138.43, 136.23, 135.20, 134.02, 133.0, 132.74, 130.63, 129.06, 122.42, 81.05, 74.72, 69.32, 69.29, 49.16; MS : (m/z) 1160 $[\text{M}]^+$, 1015 $[\text{M}-\text{C}_8\text{H}_4\text{NO}_2]^+$, 969 $[\text{C}_8\text{H}_4\text{N}_2\text{O}_4]^+$, 923 $[\text{M}-\text{C}_8\text{H}_4\text{N}_3\text{O}_4]^+$, 879 $[\text{M}-\text{C}_{10}\text{H}_8\text{N}_3\text{O}_7]^+$, 736 $[\text{M}-\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_9]^+$, 692 $[\text{M}-\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_{10}]^+$, 612 $[\text{M}-\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_{10}]^+$, 536 $[\text{M}-\text{C}_{32}\text{H}_{24}\text{N}_4\text{O}_{10}]^+$, 420 $[\text{M}-\text{C}_{37}\text{H}_{28}\text{N}_6\text{O}_{10}]^+$.

Synthesis of bis-(N-ethoxyphthalimide)-5-[(1H-benzo[d]imidazol-2-yl)methyl-3-{4-(-5-(-1H-benzo[d]imidazol-2-yl)methyl)-4-oxo-2-(4-methoxyphenyl)thioazolidin-3-yl}phenyl]-2-(4-N,N-dimethylaminephenyl)thioazolidine-4-one (5e).

IR (KBr) cm^{-1} : 3032 (C-H str., Ar-H), 1792 (str., C=O), 1733 (Str., C=O), 1610 (str. C=N), 1462 (C=C); ^1H NMR (DMSO) δ : 7.84-7.09 (m, 28H, Ar-H), 5.69 (s, 2H, CH-Ar), 4.47 ($J = 3.7 \text{ Hz}$, t, 4H, O- CH_2), 4.39 ($J = 6.1 \text{ Hz}$, t, 2H, CH), 3.94 ($J = 3.7 \text{ Hz}$, t, 4H, N- CH_2), 3.37 (s, 12H, N(CH_3)₂), 3.21 ($J = 12.7 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 3.19, ($J = 12.7 \text{ Hz}$, dd, 2H, CH_b distereotropic proton); ^{13}C -NMR (CDCl_3) δ : 172.34, 165.92, 151.16, 146.72, 143.69, 141.23, 138.34, 137.82, 136.28, 133.82, 132.57, 131.02, 130.43, 127.83, 126.29, 80.52, 73.28, 66.62, 48.31, 43.62, 41.62; MS : (m/z) 1158 $[\text{M}]^+$, 1113 $[\text{M}-\text{C}_2\text{H}_6\text{N}]^+$, 967 $[\text{M}-\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2]^+$, 923 $[\text{M}-\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3]^+$, 846 $[\text{M}-\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3]^+$,

726 $[\text{M}-\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_3]^+$, 580 $[\text{M}-\text{C}_{34}\text{H}_{32}\text{N}_4\text{O}_5]^+$, 536 $[\text{M}-\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_6]^+$, 420 $[\text{M}-\text{C}_{43}\text{H}_{40}\text{N}_4\text{O}_6]^+$, 304 $[\text{M}-\text{C}_{50}\text{H}_{44}\text{N}_6\text{O}_6]^+$.

General procedure for Synthesis of 5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3-(4-(5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2-(4-substitutedphenyl)-4-oxothiazolidin-3-yl)phenyl)-2-(4-substitutedphenyl)thiazolidin-4-one (6a-e).

Compounds (3a-e) (0.01 mole) and thiosemicarbazide (0.02 mole) were dissolved in absolute ethanol and reaction mixture was refluxed for 6 hr. Residue was recrystallized from methanol (6a-e).

Synthesis of 5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3-(4-(5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-4-oxo-2-phenylthiazolidin-3-yl)phenyl)-2-phenylthiazolidin-4-one (6a). IR (KBr) cm^{-1} : 3420, 3349 (NH_2), 3090 (C-H str., Ar-H), 2951, 2890 (CH str.), 1705 (str., C=O), 1618 (str. C=N), 1434 (C=C); ^1H NMR (DMSO) δ : 6.89-7.35 (m, 14H, ArH), 5.4 (s, 2H, CH-Ar), 4.91 (s, 4H, NH_2), 4.2 ($J = 13.2 \text{ Hz}$, dd, 2H, CH_a distereotropic proton), 4.0 ($J = 13.2 \text{ Hz}$, dd, 2H, CH_b distereotropic proton), 3.9 ($J = 5.9 \text{ Hz}$, t, 2H, CH); ^{13}C -NMR (CDCl_3) δ : 168.91, 165.01, 161.34, 135.91, 134.78, 130.56, 129.42, 125.07, 118.93, 62.51, 58.12, 33.87; MS : (m/z) 658 $[\text{M}]^+$, 558 $[\text{M}-\text{C}_2\text{H}_2\text{N}_3\text{S}]^+$, 458 $[\text{M}-\text{C}_4\text{H}_4\text{N}_6\text{S}_2]^+$, 444 $[\text{M}-\text{C}_5\text{H}_6\text{N}_6\text{S}_2]^+$, 430 $[\text{M}-\text{C}_6\text{H}_8\text{N}_6\text{S}_2]^+$, 354 $[\text{M}-\text{C}_{12}\text{H}_{13}\text{N}_6\text{S}_2]^+$, 276 $[\text{M}-\text{C}_{18}\text{H}_{18}\text{N}_6\text{S}_2]^+$, 173 $[\text{M}-\text{C}_{21}\text{H}_{20}\text{N}_7\text{OS}_3]^+$.

Synthesis of 5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3-(4-(5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)phenyl)-2-(4-chlorophenyl)thiazolidin-4-one (6b).

IR (KBr) cm^{-1} : 3440, 3359 (NH_2), 3095 (C-H str., Ar-H), 2988, 2879 (CH str.), 1711 (str., C=O), 1622 (str. C=N), 1430 (C=C), 760 (C-Cl); ^1H NMR (DMSO) δ : 7.65-7.01 (m, 12H

Ar-H), 5.52 (s, 2H, CH-Ar), 4.99 (s, 4H, NH₂), 4.4 ($J = 12.9$ Hz, dd, 2H, CH_a distereotropic proton), 4.0 ($J = 12.9$ Hz, dd, 2H, CH_b distereotropic proton), 3.82 ($J = 5.1$ Hz, t, 2H, CH); ¹³C-NMR(CDCl₃) δ: 175.01, 169.32, 162.35, 138.21, 135.29, 131.78, 130.31, 126.98, 119.54, 64.51, 56.59, 35.92; MS :(m/z) 728 [M]⁺, 730[M+2]⁺, 732[M+4]⁺, 504[M-C₁₂H₈Cl₂]⁺, 404[M-C₁₄H₁₀N₃Cl₂S]⁺, 304[M-C₁₆H₁₄N₈S₂O₄]⁺, 190[M-C₂₀H₁₆N₇OC₁₂S₃]⁺.

Synthesis of 5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3-(4-(5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)phenyl)-2-(4-methoxyphenyl)thiazolidin-4-one (6c).

IR (KBr) cm⁻¹: 3419, 3352 (NH₂), 3070 (C-H str., Ar-H), 2972, 2868 (CH str.), 1706 (str., C=O), 1612 (str. C=N), 1429 (C=C), 1253 (C-O-C); ¹H NMR (DMSO) δ 7.44-6.82 (m, 12H, Ar-H), 5.43 (s, 2H, CH-Ar), 5.01 (s, 4H, NH₂), 4.5 ($J = 12.3$ Hz, dd, 2H, CH_a distereotropic proton), 4.2 ($J = 12.3$ Hz, dd, 2H, CH_b distereotropic proton), 3.91 ($J = 5.3$ Hz, t, 2H, CH), 3.97 (s, 6H, OCH₃); ¹³C-NMR(CDCl₃) δ : 174.81, 168.12, 162.67, 160.11, 139.33, 133.78, 131.23, 122.01, 116.34, 68.91, 56.92, 54.21, 36.32; MS: (m/z): 718[M]⁺, 618[M-C₂H₂N₃S]⁺, 518[M-C₄H₄N₆S₂]⁺, 411[C₁₁H₁₁N₆S₂O]⁺, 304[M-C₁₈H₁₈N₆S₂O₂]⁺, 191[M-C₂₂H₂₂N₇S₃O₃]⁺.

Synthesis of 5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3-(4-(5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one (6d).

IR (KBr) cm⁻¹: 3462, 3390 (NH₂), 3105 (C-H str., Ar-H), 2983, 2871 (CH str.), 1713 (str., C=O), 1637 (str. C=N), 1442 (C=C), 1532-1370 (NO₂, str.); ¹H NMR (DMSO) δ: 7.81-7.22 (m, 12H, Ar-H), 5.69 (s, 2H, CH-Ar), 5.10 (s, 4H, NH₂), 4.9 ($J = 11.9$ Hz, dd, 2H, CH_a distereotropic proton), 4.5 ($J = 11.9$ Hz, dd, 2H, CH_b distereotropic proton), 4.01 ($J = 5.2$ Hz, t, 2H, CH); ¹³C-NMR (CDCl₃) δ :

177.21, 169.34, 163.78, 161.56, 145.01, 135.78, 133.86, 128.23, 117.83, 69.54, 61.82, 38.03; MS :(m/z): 748 [M]⁺, 626 [M-C₆H₄NO₂]⁺, 526 [M-C₈H₆N₄SO₂]⁺, 426[M-C₁₀H₁₀N₇S₂O₂]⁺, 304[M-C₁₆H₁₄N₈S₂O₄]⁺, 190[M-C₂₀H₂₀N₉S₃O₅]⁺.

Synthesis of 5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3-(4-(5-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)phenyl)-2-(4-(dimethylamino)phenyl)thiazolidin-4-one (6e).

IR (KBr) cm⁻¹: 3443, 3363 (NH₂), 3097 (C-H str., Ar-H), 2974, 2859 (CH str.), 1703 (str., C=O), 1632 (str. C=N), 1447 (C=C); ¹H NMR (DMSO) δ : 7.41-7.05 (m, 12H, Ar-H), 5.21 (s, 2H, CH-Ar), 4.93 (s, 4H, NH₂), 4.1 ($J = 12.5$ Hz, dd, 2H, CH_a distereotropic proton), 3.9 ($J = 12.5$ Hz, dd, 2H, CH_b distereotropic proton), 3.8 ($J = 4.8$ Hz, t, 2H, CH), 3.31 (s, 6H, N(CH₃)₂); ¹³C-NMR (CDCl₃) δ: 175.22, 168.12, 160.67, 159.87, 147.71, 132.36, 131.91, 129.62, 119.52, 68.71, 59.91, 52.44, 40.61; MS: (m/z) 744[M]⁺, 624 [M-C₈H₁₀N]⁺, 526 [M-C₈H₆N₄SO₂]⁺, 426 [M-C₁₀H₁₀N₇S₂O₂]⁺, 304[M-C₁₆H₁₄N₈S₂O₄]⁺, 190[M-C₂₀H₂₀N₉S₃O₅]⁺.

Result and Discussion

Substituted N,N'-bis[(phenyl)methylidene] benzene-1,4-diamine **2a-e** have been by the condensation reaction of p-phenyldiamine with various arylaldehyde **2a-e**. Additionally when **2a-e** were reacted with mercaptosuccinic acid, it gave 2,2'-[benzene-1,4-diylbis{2-(phenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}]diacetic acid **3a-e**. The IR Spectrum of the compound **3a** shows bands 2705 cm⁻¹ due to OH, stretching of COOH group, as expected for the formation of compound **3a**, which was confirmed by ¹H NMR spectrum. In addition to it, we found a peak at δ 10.5 singlet, which showed the present of OH group. Further the reaction involving synthesis of 5-[(1H-benzo[d]imidazol-2-yl)methyl]-3-{4-(5-(-1H-benzo[d]imidazol-2-yl) methyl)-

4-oxo-2-phenylthioazolidin-3-yl}phenyl]-2-phenylthioazolidine-4-one **4a-e** took place by reacting 2,2'-[benzene-1,4-diylbis{2-(phenyl-4-oxo-1,3-thiazolidine-3,5-diyl)}] diacetic acid **3a-e** with *o*-phenylenediamine. Formation of this compound was confirmed by N-H stretching at 3370 in IR region and characteristic peak at δ 6.21 in ¹HNMR for NH group. Compound **4a** were reacted with bromoalkoxy phthalimide to gave **5a** as shown by new two triplets peak of 4.44-4.41(t, O-CH₂) and 3.90-3.83 of (t, N-CH₂) groups in NMR region and compounds were confirmed by disappearance of NH peak in IR and NMR region. In another route compounds **3a** converted into **6a** by treatment with thiosemicarbazide and give final product. Formation of this compound was confirmed by IR frequency of NH₂ group at 3420, 3349 cm⁻¹.

Antiviral activity

The antiviral activities of compounds **5 (a-e)** and **6 (a-e)** were evaluated against a variety of viruses (**Table 1 & Table 2**). The following viruses and host cells were used for the evaluation: (a) HeLa cell cultures: vesicular stomatitis virus, Coxsackie B4 virus, and respiratory syncytial virus (RSV). (b) HEL cell cultures: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), herpes simplex virus-1 (TK-KOS ACVR), vaccinia virus (VV), and vesicular stomatitis virus (VSV) in (**Table 1**). For each compound, the minimum inhibitory concentration (MIC) and the minimal cytotoxic concentration (MCC) or the cytotoxic concentration required to reduce cell growth by 50 % (CC₅₀), were obtained.

(S)-9-(2,3-dihydroxypropyl)adenine [(S)-DHPA], ribavirin, acyclovir, cidofovir and ganciclovir were used as the reference compounds. In the tests with viruses described in (a), (b), and (c) antiviral activity and, in parallel, cytotoxicity were monitored with the compound concentrations up to 200 μ M. The cut-off point for specific antiviral activity was

5-fold lower than the cytotoxic concentration (MCC or CC₅₀).

All synthesized compounds were also screened against cytomegalovirus (CMV) [strains AD-169 and Davis], varicella-zoster virus (VZV) [TK+ VZV strain OKA, and TK- VZV strain 07/1] in human embryonic lung (HEL) cells **Table 2**. Compound **5d** was found active against AD-169 is **10.34** μ g/ml, and Davis strains of cytomegalovirus is **8.91**. Whereas cytotoxicity (MCC) of this compound in HEL cells was observed at **150** μ g/ml. Another active derivative was compound **6e**, which inhibited AD-169 strain of CMV and thymidine kinase positive varicellazoster virus (TK+VZV, OKA strain) at an EC₅₀ value of **4.1** μ g/ml and **5.3** μ g/ml, respectively. Compounds **5e** and **6a** show activity against Antiviral activity EC₅₀ (μ g/ml) (TK- VZV 07/1 strain) value of **6.07** μ g/ml and **5.90** μ g/ml respectively.

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Reaction Scheme

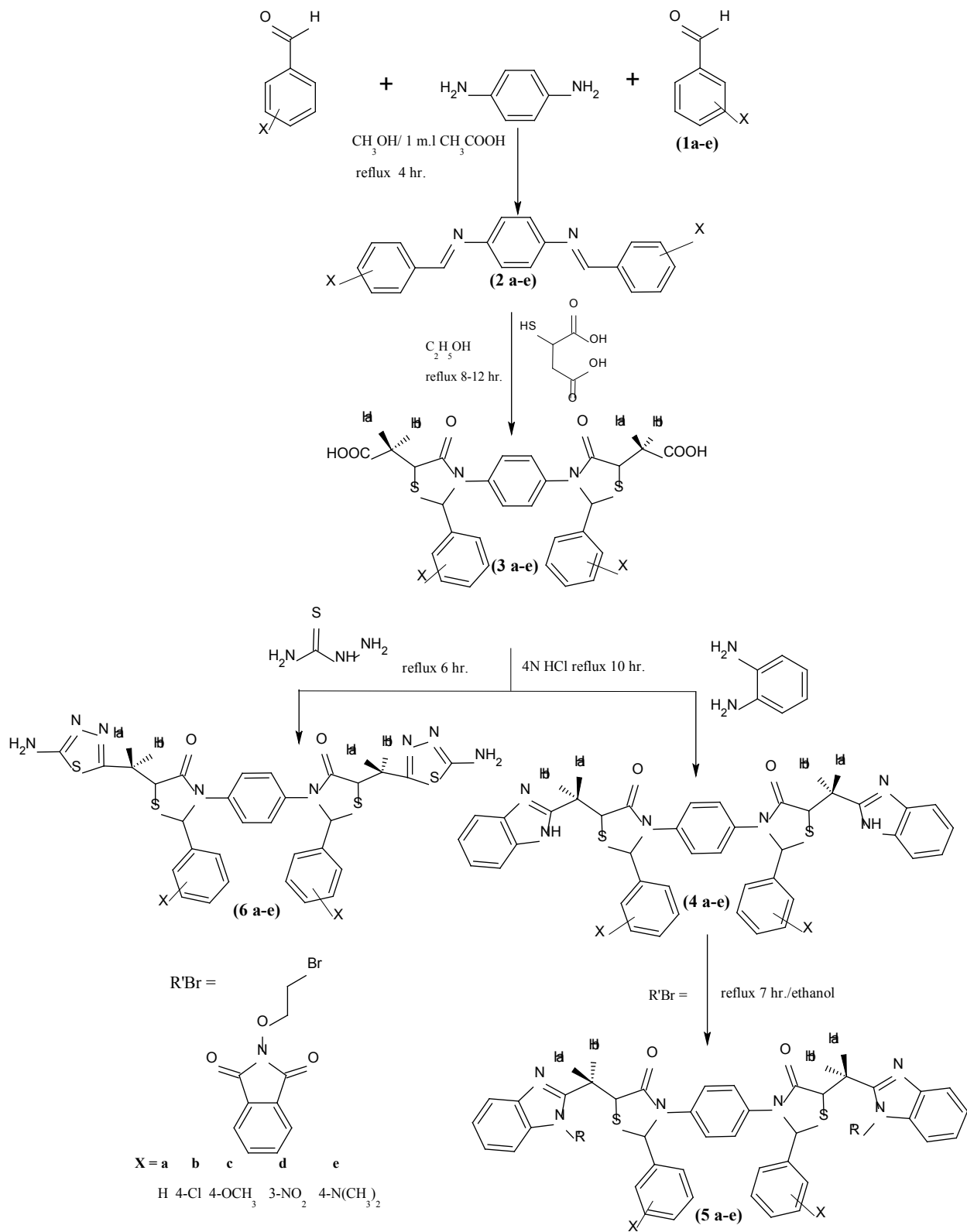


Table 1: **Cytotoxicity and antiviral activity of compounds 5 (a–e) and 6 (a–e) in HEL and HeLa cell cultures**

Comp.	HEL cell cultures						HeLa cell cultures			
	Min inhibitory conc. b (µg/ml)						Min inhibitory conc. b (µg/ml)			
	Min cytotoxic conc. ^a (µg/ml)	HSV-1 (KOS)	HSV-2 (G)	Vaccina virus	Vesicular stomatitis virus	HSV-1 TK KOSACV ^r	Min inhibitory conc. ^b (µg/ml)	Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
5a	>100	>50	>100	>100	>100	50	>200	>150	>50	>100
5b	>100	>50	>100	>100	>50	>30	>100	>50	>40	>50
5c	>150	>100	>50	>50	>40	40	>150	>100	>20	>80
5d	>100	40	>40	>50	>30	>50	100	>100	>15	>50
5e	>200	>100	>50	>100	>40	30	50	>40	>50	10
6a	100	>50	>100	>50	>20	>30	40	20	>15	8
6b	>50	>40	>20	>20	>40	15	>100	>50	>100	>40
6c	>100	>40	50	>40	35	>100	>150	>50	>40	>150
6d	>100	>40	>50	>40	30	>10	>100	>50	35	>80
6e	>100	>30	>40	>50	>40	35	50	>40	>20	>15
Brivudin (µM)	>250	0.08	20	10	>200	>250	>250	>250	>250	>250
Ribavirin (µM)	>250	>250	>150	>150	>100	40	50	30	150	50
Acyclovir (µM)	>250	0.4	0.4	>150	>250	50	-	-	-	-
Ganciclovir (µM)	>100	.032	.0064	100	>100	2.4	-	-	-	-
(S)-DHPA (µM)	—	—	—	—	—	—	>250	150	150	>250

a Required to cause a microscopically detectable alteration of normal cell morphology.

b Required to reduce virus-induced cytopathogenicity by 50 %.

Table 2: Cytotoxicity and antiviral activity of compounds 5 (a–e) and 6 (a–e) against cytomegalovirus (CMV) and Varicella-zoster virus (VZV) in human embryonic lung (HEL) cells.

Comp.	Antiviral activity EC50 (µg/ml) ^a		Cytotoxicity (µg/ml)		Antiviral activity EC50 (µg/ml) ^a		Cytotoxicity (µg/ml)	
	CMV AD-169 strain	CMV Davis strain	Cell morphology (MCC) ^b	Cell growth (CC50) ^c	TK+ VZV OKA strain	TK– VZV 07/1 strain	Cell morphology (MCC) ^b	Cell growth (CC50) ^c
5a	>10	>20	>50	>55	>100	>100	>100	>100
5b	>100	>50	>100	>100	>50	>100	>100	>100
5c	>100	>100	>100	>100	>100	>100	>100	>100
5d	10.34	8.91	>20	>25	>20	>10	>50	18
5e	>15	>10	>15	>20	>10	6.07	>20	>15
6a	>20	>10	>15	>40	20.5	5.9	20	20
6b	>30	>20	>20	>50	>20	>25	>40	>50
6c	>40	>100	>100	>60	>10	>50	100	15
6d	>20	>10	>50	>20	>20	>20	>50	15
6e	4.1	>5	>20	>15	5.3	>10	>10	>15
Ganciclovir	1.4	1.7	400	80	-	-	-	-
Cidofovir	0.24	0.37	400	57	-	-	-	-
Acyclovir	-	-	-	-	1	15	>50	190
Brivudin	-	-	-	-	.0096	12.6	>50	244

a: Effective concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU).

b: Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.

c: Cytotoxic concentration required to reduce cell growth by 50%.

Table.3 Physical data and element analysis of synthesized compounds

Compd.	X	Molecular Weight	M. formula	m.p.	Yield	N%.	
						Calc.	Found
(2a)	H	284	C ₂₀ H ₁₆ N ₂	112	92	9.85	9.78
(2b)	Cl	353	C ₂₀ H ₁₄ N ₂ Cl ₂	145	93	7.93	7.93
(2c)	OCH ₃	344	C ₂₂ H ₂₀ N ₂ O ₂	123	89	8.13	8.19
(2d)	NO ₂	374	C ₂₀ H ₁₄ N ₄ O ₂	132	96	14.97	14.82
(2e)	N(CH ₃) ₂	370	C ₂₄ H ₂₆ N ₄	122	91	15.12	15.01
(3a)	H	548	C ₂₈ H ₂₄ N ₂ O ₆ S ₂	75	89	5.11	5.31
(3b)	Cl	617	C ₂₈ H ₂₂ Cl ₂ N ₂ O ₆ S ₂	82	86	4.54	4.63
(3c)	OCH ₃	608	C ₃₀ H ₂₈ N ₂ O ₈ S ₂	94	88	4.60	4.72
(3d)	NO ₂	638	C ₂₈ H ₂₂ N ₄ O ₁₀ S ₂	90	82	5.63	5.74
(3e)	N(CH ₃) ₂	634	C ₃₂ H ₃₄ N ₄ O ₆ S ₂	82	80	8.83	8.72
(4a)	H	692	C ₄₀ H ₃₂ N ₆ O ₂ S ₂	140	91	12.13	12.30
(4b)	Cl	761	C ₄₀ H ₃₀ Cl ₂ N ₆ O ₂ S ₂	152	93	11.03	10.89
(4c)	OCH ₃	752	C ₄₂ H ₃₆ N ₆ O ₄ S ₂	155	95	11.16	11.03
(4d)	NO ₂	782	C ₄₀ H ₃₀ N ₈ O ₆ S ₂	162	90	14.31	14.23
(4e)	N(CH ₃) ₂	778	C ₄₄ H ₄₂ N ₈ O ₂ S ₂	147	91	14.38	14.41
(5a)	H	1071	C ₆₀ H ₄₆ N ₈ O ₈ S ₂	197	89	10.46	10.23
(5b)	Cl	1140	C ₆₀ H ₄₄ Cl ₂ N ₈ O ₈ S ₂	203	88	9.83	9.98
(5c)	OCH ₃	1131	C ₆₂ H ₅₀ N ₈ O ₁₀ S ₂	205	82	9.91	9.76
(5d)	NO ₂	1161	C ₆₀ H ₄₄ N ₁₀ O ₁₂ S ₂	211	83	12.06	12.23
(5e)	N(CH ₃) ₂	1157	C ₆₄ H ₅₆ N ₁₀ O ₈ S ₂	223	84	12.10	12.21
(6a)	H	658	C ₃₀ H ₂₆ N ₈ O ₂ S ₄	262	91	17.01	16.81
(6b)	Cl	728	C ₃₀ H ₂₄ ClN ₈ O ₂ S ₄	251	94	15.40	15.35
(6c)	OCH ₃	718	C ₃₂ H ₃₀ N ₈ O ₄ S ₄	278	89	15.59	15.43
(6d)	NO ₂	748	C ₃₀ H ₂₄ N ₁₀ O ₆ S ₄	264	88	18.70	18.57
(6e)	N(CH ₃) ₂	744	C ₃₄ H ₃₆ N ₁₀ O ₂ S ₄	294	84	18.80	18.73

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