Design and synthesis of a novel 5-\((\text{aminomethylene})\text{thiazolidine-2,4-dione}\) derivatives as potent hepatitis-B virus polymerase inhibitors

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Abstract

A series of novel thiazolidinedione analogues (TZD) were designed and synthesized potent inhibitors of HBV capsid assembly. The synthesis of thiazolidine-2,4-dione derivatives (4a-4o), starting from the condensation of 5-\((\text{ethoxymethylene})\text{thiazolidine-2,4-dione}\) (1) with various secondary amines (3) derived from biologically active compounds. The newly synthesized TZD analogues 4a-4o were characterized by \(^1\)H NMR, \(^13\)C NMR, and MS and evaluated for their anti-HBV activity. Most of the compounds inhibited the expression of viral antigens at low concentration. Six compounds, 4g, 4h, 4i, 4m, 4n, and 4o, demonstrated potent inhibition of HBV DNA replication at the submicromolar range. Of these five initial hits, compound 4o was the most active when compared with lamivudine.

Introduction

Worldwide more than two billion people were seriously affected by hepatitis B virus (HBV), which can cause liver cirrhosis and hepatocellular carcinoma in humans. It was estimated that 400 million people were chronically infected with HBV worldwide up to recent times, and HBV was responsible for 750,000 deaths each year (Custer et al., 2004). HBV infections in developing countries increase abnormally. The current therapies including vaccines, immunomodulators, interferon-\(\alpha\), polyethylene glycol interferon-\(\alpha\) and nucleoside drugs for treating HBV are still unsatisfactory, due to high recurrence, drug resistance and inevitable side effects including influenza-like illness, myalgia, headache, reduction of neutrophil granulocyte and blood platelet, etc (Sato et al., 2010; Locarnini et al., 2006; Wong et al., 1993; Fattovich et al., 1988). Therefore, it is interesting to explore novel classes of drugs with different antiviral targets and mechanisms for anti-HBV purposes.

On the other hand, the thiazolidinedione analogues were investigated for the treatment of a variety of diseases, e.g., as anti-cancer (Havrylyuk et al., 2009), anti-HIV (Rawal et al., 2005), anti-ischemic (Adachi et al., 1999), anticonvulsant (Ergenç et al., 1994), antimicrobial (Piscopo et al., 1989), antihistaminic (Previtera et al., 1994; Diurno et al., 1999), and antidiabetic agents (Carroll et al., 2011; Bruno et al., 2002), 15-hydroxy prostaglandin dehydrogenase inhibitors (Wu et al., 2011; Zidar et al., 2010), inhibitors of MurD ligase (Ha et al., 2012), aldose reductase inhibitors (Ma et al., 2012), for their anti-obesity effects (Bhattarai et al., 2010).

The thiazolidinediones affect genes and the specific gene expression profile induced by each of these molecules resulting in different activities for the thiazolidinedione derivatives. This observation has encouraged many medicinal and synthetic chemists to modify thiazolidinedione chemistry and utilize this core to synthesize numerous novel compounds with various pharmacological and therapeutic activities. The list of effects induced by the thiazolidinedione analogues is far from complete and needs specific attention. However, considering the broad therapeutic potential, this five-membered heterocyclic ring (thiazolidine-2,4-dione 4) will play an important role in future...
Materials and Methods

Chemistry: Chemicals and solvents were purchased either from Fluka or Merck, and all reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates and visualized under UV light. 1H NMR spectra were recorded with a Varian Mercury Plus 400 MHz instrument. 13C NMR spectra were recorded on a Varian Gemini 100 MHz instrument. Signals due to the solvent (13C NMR) or residual protonated solvent (1H NMR) served as the internal standard. All the chemical shifts are reported in δ (ppm) using TMS as an internal standard. Multiplicity is indicated by one or more of the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the coupling constants (J) correspond to the order of the multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under a nitrogen atmosphere.

Synthesis of 5-((ethoxymethyl)thiazolidine-2,4-dione (1): Pale yellow solid; yield: 98%; m.p.: 83–91°C; IR (KBr): umax 3383, 3104, 2989, 2423, 1721, 1677, 1473, 1392, 1229, 1105, 1010, 867, 740, 691 cm-1; 1H NMR (400 MHz, DMSO-d6): δ 8.38 (brs, 1H), 7.65 (s, 1H), 4.20 (q, J = 5.4 Hz, 2H), 1.40 (t, J = 5.4 Hz, 3H) ppm; ESI-MS: m/z calcd for C15H14NO4S ([M+H]+) 272, found 272.0922.

General experimental procedure for the synthesis of TZD derivatives (4a–4o): To a suspension of 1 (100 mg, 0.58 mmol) in acetonitrile was added secondary amines (0.58 mmol) in one lot. The reaction mixture was stirred at room temperature for 15–20 min, and the completion of the reaction was monitored by TLC. The precipitated solids were filtered at the pump and dried to obtain the pure compounds in quantitative yields.

(Z)-5-((4-tert-butyl-piperazin-1-yl)methylene)thiazolidine-2,4-dione (4e): White solid; yield: 98%; m.p.: 72–78°C; 1H NMR (400 MHz, DMSO-d6): δ 11.56 (brs, 1H), 7.60 (s, 1H), 3.46–3.38 (m, 8H), 1.40 (s, 9H) ppm; 13C NMR (100 MHz, DMSO-d6): δ 167.9, 167.2, 153.5, 142.8, 86.7, 79.3 (2C), 49.3 (2C), 27.1 (4C) ppm; ESI-HRMS: m/z calcd for C30H38N2O6S ([M+H]+) 670.2692, found 670.2691.

(Z)-5-((4-tert-butyl-4-dioxothiazolidin-5-ylidene)methyl)propylamine (4f) White solid; yield: 90%; m.p.: 61–62°C; 1H NMR (400 MHz, CDCl3): δ 11.58 (s, 1H), 8.02–7.84 (m, 4H), 7.62–7.58 (m, 3H), 7.40 (s, 1H), 5.10 (s, 2H), 3.15 (s, 3H) ppm; 13C NMR (100 MHz, CDCl3): δ 168.5, 167.3, 144.6, 133.4, 131.4 (2C), 130.5, 128.7, 128.3 (2C), 126.6 (2C), 126.1 (2C), 125.5, 122.9, 87.0 ppm; ESI-HRMS: m/z calcd for C22H18N2O6S ([M+H]+) 528.1170, found 528.1172.

(Z)-5-((4-tert-butyl-4-dioxothiazolidin-5-ylidene)methyl)propylamine (4f) White solid; yield: 90%; m.p.: 61–62°C; 1H NMR (400 MHz, CDCl3): δ 11.58 (s, 1H), 8.02–7.84 (m, 4H), 7.62–7.58 (m, 3H), 7.40 (s, 1H), 5.10 (s, 2H), 3.15 (s, 3H) ppm; 13C NMR (100 MHz, CDCl3): δ 168.5, 167.3, 144.6, 133.4, 131.4 (2C), 130.5, 128.7, 128.3 (2C), 126.6 (2C), 126.1 (2C), 125.5, 122.9, 87.0 ppm; ESI-HRMS: m/z calcd for C22H18N2O6S ([M+H]+) 528.1170, found 528.1172.

(Z)-5-((4-tert-butyl-4-dioxothiazolidin-5-ylidene)methyl)propylamine (4f) White solid; yield: 90%; m.p.: 61–62°C; 1H NMR (400 MHz, CDCl3): δ 11.58 (s, 1H), 8.02–7.84 (m, 4H), 7.62–7.58 (m, 3H), 7.40 (s, 1H), 5.10 (s, 2H), 3.15 (s, 3H) ppm; 13C NMR (100 MHz, CDCl3): δ 168.5, 167.3, 144.6, 133.4, 131.4 (2C), 130.5, 128.7, 128.3 (2C), 126.6 (2C), 126.1 (2C), 125.5, 122.9, 87.0 ppm; ESI-HRMS: m/z calcd for C22H18N2O6S ([M+H]+) 528.1170, found 528.1172.
(Z)-5-((Methyl(3-phenyl-3-(o-tolyloxyl)propyl)amino)methylene)thiazoypeptide-2,4-dione (4): White solid; yield: 96%; m.p.: 129–130°C; ¹H NMR (400 MHz, CDCl₃): δ 11.60 (br, s, 1H), 7.58 (s, 1H), 7.40–7.22 (m, 5H), 7.18–7.15 (m, 1H), 7.04–6.90 (m, 1H), 6.78–6.66 (m, 2H), 5.40 (br, m, 1H), 4.22 (t, J = 6.6 Hz, 2H), 3.06 (s, 3H), 2.36 (s, 3H), 1.24 (t, J = 6.6 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 167.2, 155.1, 144.4, 141.2, 129.6 (2C), 129.4 (2C), 128.5 (3C), 127.6, 126.0 (2C), 115.7 (2C), 76.4, 36.6 (2C), 20.0 ppm; ESI-HRMS: m/z calc'd for C₉ᴴ₂₀N₂O₇S₃ ([M+H]+) 3831443, found 3831442.

(Z)-5-((Methyl(3-phenylpropyl)amino)methylene)thiazoypeptide-2,4-dione (4): Pale yellow solid; yield: 90%; m.p.: 117–118°C; ¹H NMR (400 MHz, CDCl₃): δ 11.56 (br, s, 1H), 7.60 (s, 1H), 7.38–7.18 (m, 5H), 3.40 (t, J = 5.2 Hz, 2H), 3.10 (s, 3H), 2.62–2.50 (t, J = 7.6 Hz, 2H), 1.90–1.80 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 167.2, 144.4, 141.0, 128.3 (3C), 128.2 (3C), 125.8, 31.8, 29.5 ppm; ESI-HRMS: m/z calc'd for C₁₄H₁₆N₂O₇S ([M+H]+) 2771014, found 2771005.

(Z)-5-((4-((2-Chlorophenyl)phenyl)methyl)piperazin-1-yl)methylene)thiazoypeptide-2,4-dione (4K): White solid; yield: 89%; m.p.: 92–94°C; ¹H NMR (400 MHz, CDCl₃): δ 7.80 (d, J = 8 Hz, 1H), 7.52 (s, 1H), 7.40–7.20 (m, 8H), 4.80 (s, 1H), 3.50 (br, m, 4H), 2.46–2.20 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 148.7, 168.2, 121.4, 140.1, 139.2, 132.7, 129.6, 128.7, 128.6, 128.5, 128.1, 127.7, 127.4, 87.5, 67.9, 51.2, 49.6, 45.6, 40.1, 38.8, 11.40 ppm; ESI-HRMS: m/z calc'd for C₁₄H₁₆N₂O₂Cl ([M+H]+) 4141057, found 4141038.

(Z)-5-((4-(2,3-Dichlorophenyl)phenyl)methyl)piperazin-1-yl)methylene)thiazoypeptide-2,4-dione (4M): White solid; yield: 96%; m.p.: 88–89°C; ¹H NMR (400 MHz, CDCl₃): δ 11.60 (s, 1H), 7.62 (s, 1H), 7.38 (m, 2H), 7.20 (dd, J = 6.6 Hz, 1H), 3.62–3.60 (m, 4H), 3.16–3.02 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 168.0, 150.3, 142.9, 132.6, 128.5 (2C), 126.1, 124.9, 120.0, 86.6, 50.7 (4C) ppm; ESI-HRMS: m/z calc'd for C₁₄H₁₂N₂O₂Cl ([M+H]+) 3580186, found 3580178.

(Z)-5-((4-(Benzo[d]isothiazol-3-yl)piperazin-1-yl)methylene)thiazoypeptide-2,4-dione (4N): Yellow solid; yield: 94%; m.p.: 118–119°C; ¹H NMR (400 MHz, CDCl₃): δ 11.30 (br, s, 1H), 8.10 (d, J = 8.4, 1H), 8. (d, J = 8.4, 1H), 7.70 (s, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 3.76 (m, 4H), 3.58 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 167.8, 162.7, 152.0, 142.9, 128.0, 127.0, 124.4 (2C), 124.1, 121.0, 86.8, 49.3 (4C) ppm; ESI-HRMS: m/z calc'd for C₁₅H₁₄N₂O₂S₂ ([M+H]+) 3470645, found 3470631.

Cell culture: HepG2 2.2.15 cells, derived from HepG2 human hepatocellular carcinoma cells, were stably transfected with a head-to-tail HBV DNA dimer and were maintained in MEM with heat-inactivated 10% fetal bovine serum (FBS) and 1% antibiotics. In parallel experiments, human Huh7 hepatoma cells were maintained in Dulbecco’s modified Eagle medium (DMEM) supplemented with heat-inactivated 10% FBS and 1% antibiotics. HepG2 2.215 and Huh7 cells were both grown at 37°C in a humidified atmosphere of 5% CO₂ and 95% air.

Cell viability assay: The cytotoxic effects of IN-4 (5) were determined using a Cell Titer 96 cell proliferation assay kit (MTS) (Promega, USA). In order to pinpoint the toxicity limits in HepG2 2.2.15 and Huh7 cells, they were plated into 96-well plates at a density of 4 x 10⁴ cells/mL for 24 hours. Cells were then treated with serial dilutions of IN-4 (5), ranging 2.5–160 mg/mL, and the mixture was incubated for 3 days. Cell toxicity was measured according to the manufacturer’s protocol. All measurements were performed in four replicates, and results are presented as relative percentages over that of the control group.

**Determination of HBV expression levels:** After treating HepG2 2.2.15 cells or HBV-transfected Huh7 cells, levels of the HBsAg and HBeAg proteins were measured in culture media using an EIA kit (Johnson and Johnson, USA) according to the manufacturer’s instructions.

**SEC general procedure:** Capsid assembly was initiated by mixing Cp149 with test compounds in 2 buffer incubation 24 hours, respectively. Assembly reactions were examined on a Superose column (Biosep-SEC-S3000) mounted on HPLC system equipped with an auto injection module. The column was equilibrated with 100 mM HEPES pH 7.5, 300 mM NaCl at 0.6 mL/min.
Results and Discussion

The synthesis of a novel series of substituted 5-(aminomethylene)thiazolidine-2,4-diones (compounds 4a-4o) is shown in Scheme 1. In the first step, thiazolidine-2,4-dione 1 was reacted with triethyl orthoformate in the presence of Ac₂O at reflux temperature afforded 5-(ethoxymethylene)thiazolidine-2,4-dione 2 as a pale yellow crystalline solid (Lo et al., 1954). The condensation of 1 with various secondary amines in ethanol at reflux temperature resulted 5-(aminomethylene)thiazolidine-2,4-diones in good yields. The secondary amines were obtained from different commercial sources. Thus, the structures of the synthesized target compounds are listed in Table I.

Inhibition activities for HBV replication of the compounds 4a-4o were determined in the HepG2.2.15

![Scheme 1: Synthesis of 5-(aminomethylene)thiazolidine-2,4-diones](image)

| Table I |
|------------------|------------------|------------------|------------------|
| Synthesis of a novel series of substituted 5-(aminomethylene)thiazolidine-2,4-diones<sup>a</sup> |
| Entry | 2<sup>b</sup> Amine (3) | Product | Yield<sup>b</sup> (%) |
|-------|------------------|------------------|------------------|
| 1     |                  | ![4a](image)     | 98               |
| 2     |                  | ![4b](image)     | 97               |
| 3     |                  | ![4c](image)     | 91               |
| 4     |                  | ![4d](image)     | 98               |
| Entry | 2° Amine (3) | Product | Yield (%) |
|-------|--------------|---------|-----------|
| 5     | ![Structure 5](image5) | ![Structure 4e](image4e) | 96        |
| 6     | ![Structure 6](image6) | ![Structure 4f](image4f) | 91        |
| 7     | ![Structure 7](image7) | ![Structure 4g](image4g) | 87        |
| 8     | ![Structure 8](image8) | ![Structure 4h](image4h) | 92        |
| 9     | ![Structure 9](image9) | ![Structure 4i](image4i) | 95        |
| 10    | ![Structure 10](image10) | ![Structure 4j](image4j) | 91        |
| 11    | ![Structure 11](image11) | ![Structure 4k](image4k) | 88        |
cells, which constitutively produces HBV genomes, and secretes virus-like particles (Korba et al., 1992). Lamivudine (3TC) was used as positive control. To ascertain the cytotoxic effects of the tested compounds, the cell viability was determined after the cells exposed to the compounds for 48 hours (Table II).

Hep G2.2.15 cell contained multiple copies of the HBV genome, which were stably integrated into the host cell genome and was widely used as a useful ‘in vitro’ model for evaluation of novel anti-HBV drugs. So, in the experiment, the Hep G2.2.15 cell line as in vitro cellular model was chosen.

All the target compounds were tested in vitro in HepG2.2.15 cells for anti-HBV activity and cytotoxicity. The properties of synthesized compounds are summarized in Table II, in which they are compared to the drug lamivudine. Compounds 4g, 4h, 4l, 4m, 4n, and 4o displayed good to better anti HBV activity.

A comparison of the IC_{50} values of the derivatives 4a-4o clearly indicated that the size and polarity of substituent on the substitution had noticeable effect on its antiviral activities (Table II). 4l (IC_{50} = 6.66 µM), bearing a (Z)-5-((4-(4-chlorophenyl)(phenyl) methyl) piperazine group, was more potent inhibitor of HBV replication than 3TC (13.87 µM). When the attachments on TZD was replaced by rigidified piperazinyl derivatives to give compounds 4k, 4m, 4n, 4o (the IC_{50} values 18.3, 6.3, 4.3 and 3.2 µM respectively), their anti-HBV activities were reserved or even improved. Replacing the piperizine attachment atom of N-methyl side chain containing nucleus in the compounds 4e to 4j there is no improvement in anti-HBV activity. There is no effect on the anti HBV activity when the TZD compound was substituted with piperidine or piperazine derivatives 4a to 4d. In the five ‘piperazinyl’ derivatives, 4k (IC_{50} = 18.3 µM), 4l (IC_{50} = 6.7 µM), 4m (IC_{50} = 6.3 µM), 4n (IC_{50} =4.3 µM) and 4o (IC_{50} = 3.2 µM) also showed high inhibition of HBV replication, however, When there is no attachment on piperazine, such as 4c and 4d, both of them gave none antiviral

| Entry | 2° Amine (3) | Product | Yield\(^a\) (%) |
|-------|--------------|---------|-----------------|
| 12    | ![Chemical Structure](image1) | ![Chemical Structure](image2) | 97              |
| 13    | ![Chemical Structure](image3) | ![Chemical Structure](image4) | 95              |
| 14    | ![Chemical Structure](image5) | ![Chemical Structure](image6) | 93              |
| 15    | ![Chemical Structure](image7) | ![Chemical Structure](image8) | 90              |

\(^a\)Compound 2 (1 mmol.), compound 3 (1 mmol.), acetonitrile (10 vol.), RT, 15-20 min; \(^b\)Isolated yields
activity. It illuminated that the anti-HBV activity largely depends on the size, length and character of TZD substituent.

Among all the compounds 4m, 4n, and 4o which are showing better anti-HBV activities, compounds containing the electron-withdrawing groups such as fluoro or chlorine are more effective than heterocyclic systems.

To gain better understand into the mechanisms of our compounds, 4o was investigated to examine the effect on preformed HBV capsid and on HBV capsid assembly by size exclusion chromatography (Stray et al., 2005). Recovered protein was assigned to the void (aberrant capsid induced by 4o, 8.5 min), capsid (9.5 min) and dimer (12.5 min) based on the HPLC chromatogram.

By SEC, we had observed the effect of compounds 4o on Cp149 (Figure 1). There was no change of the capsid morphology detected at low concentration of 4o (Cp149:4o = 4:1 or 2:1). At higher concentration (Cp149:4o = 1:2 or 1:4), the increasing continuous spectrum of void and the decreasing dimmers were observed. The results suggested that 4o can break the equilibrium and change the product of HBV core protein self-assembly. By structural biology, we established a screening system for anti-HBV compounds that target on nucleocapsid. SEC would be a much better method to discover the strong antiviral compounds because of its objectivity, convenience and precision.

**Conclusion**

The newly synthesized TZD analogues 4a-4o were evaluated for their anti-HBV activity, which provided 5 active derivatives inhibiting HBsAg secretion, 6 active derivatives suppressing HBeAg secretion and 5 active derivatives inhibiting HBV DNA replication. Interestingly, compound 4o could inhibit not only HBsAg and HBeAg secretions but also HBV DNA replication with SI values of 41, 123.4 and 286.

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**Conflict of Interest**

Authors declare no conflict of interest

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