



## Synthesis and Characterization of Novel Thiazolidine-2,4-dione (TZD) Derivatives with Hexyl and Decyl Chains

Troy Justine L. Ignacio, Vladimir Eli C. Taopo, Glenn Kelly U. Tan, Virgilio D. Ebajo Jr., Glenn V. Alea\*

Chemistry Department, De La Salle University, 2401 Taft Avenue, Manila, Philippines

\*Corresponding author: glenn.alea@dlsu.edu.ph

**Abstract:** Thiazolidine-2,4-dione (TZD) and some of its derivatives are known to prevent and potentially cure some diseases such as type 2 diabetes mellitus and various kinds of cancer. Two novel thiazolidine-2,4-dione (TZD) derivatives (**S3P1** and **S3P3**) with straight alkyl chain moieties were synthesized and characterized. The synthesis of the compounds involved the tosylation of hexanol and decanol giving alkyl tosylates **S1P1** and **S1P3** respectively. Nucleophilic substitution reaction between the alkyl tosylates and *p*-hydroxybenzaldehyde (PHB) formed the precursor compounds 4-alkyloxybenzaldehyde products **S2P1** and **S2P3**. Coupling each of the latter compounds with TZD utilizing Knoevenagel condensation produced the final products, 5-(4-alkyloxybenzylidene)thiazolidine-2,4-diones **S3P1** (**82.03%**) and **S3P3** (**41.45%**).

Infrared spectroscopy, mass spectrometry, and NMR spectroscopy were used in the characterization of the TZD derivatives. IR and MS were used to confirm the structure of the precursor compounds.

**Keywords:** thiazolidine-2,4-dione; *p*-hydroxybenzaldehyde; heterocycles; Knoevenagel condensation

### 1. INTRODUCTION

Diabetes mellitus, or simply diabetes, is one of the most common diseases in the present times. There are about 387 million people around the world suffering from diabetes and it is estimated that this

number will increase to 592 million by the year 2035. Diabetes caused 4.9 million deaths in 2014, which translates to a person dying from diabetes every 7 seconds, and the greatest number of cases occurs to people aged 40-59 (International Diabetes Foundation [IDF], 2014). Combating this disease



requires the help of synthetic medicines. The design, synthesis and production of molecules that have human therapeutic value with little to no side-effects post challenges to researchers.

A strategy used in developing new potential drugs is known as Structure-Activity Relationship (SAR) studies. In this method, the structure of a compound with a known bioactivity is manipulated and the resulting compound's bioactivity is tested and compared with the original (Jaworska and Nikolova, 2004). Application of this study may result in the discovery of drugs of increased potency with fewer side-effects.

Thiazolidinedione (thiazolidone-2,4-dione), simply known as TZD, is a molecule of interest regarding SAR studies. TZD and some of its derivatives are known to be a preventive and potential cure to some diseases such as diabetes mellitus (Type 2 diabetes) and various kinds of cancer including lung, breast and colon cancers. It has also displayed antimicrobial and anti-inflammatory properties (Malik, Upadhaya, & Miglani, 2011).

The scope of this study is the synthesis and characterization of new TZD derivatives with different lengths of alkyl chains. The introduction of the aliphatic groups will increase the lipophilicity of the derivatives. It is expected that the new compounds can better penetrate the cell membrane to reach its target site.

## 2. METHODOLOGY

### 2.1. Materials, Reagents, and Apparatus

In the synthesis of thiazolidine-2,4-dione derivatives, all the reagents used were analytical grade purchased from Sigma-Aldrich Chemicals.

The 550 Nicolet FT-IR Spectrophotometer was used to obtain the necessary infrared spectra of the compounds. Electron spray ionization mass spectra of the compounds were determined using the Brüker

LC-MS microTOF-Q III set at either positive or negative ion polarity. The final products were sent to the University of the Philippines – Diliman for nuclear magnetic resonance analysis using Agilent Varian 500MHz. Thin-layer chromatography experiments were done to visually determine the purity of the products using Fluka silica gel plates. The spots in the silica plates were visualized with the use of ultraviolet light and iodine-silica chamber (I<sub>2</sub>). Fischer-Johns Melting Point Apparatus was used to determine the melting point of solid products. All intermediates and final products were subjected to rotary evaporation for removing solvents.

### 2.2. General Procedures for the Synthesis of Alkyl Tosylates

Solvent-free conditions patterned from Kazemi et al. (2007) was used in forming tosylates of corresponding primary alcohol (1-hexanol or 1-decanol). The corresponding alcohol together with dry potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) and *p*-toluenesulfonyl chloride (TsCl) were crushed and mixed vigorously in a mortar for about 5 minutes. To eliminate the excess TsCl, potassium hydroxide (KOH), was added to the mixture and mixed vigorously for 2 minutes. A drop of *t*-butanol was added after mixing to quench the reaction. The resulting alkyl tosylate was extracted using five (5) 10-mL portions of diethyl ether (Et<sub>2</sub>O). The extracted mixture was filtered and concentrated using vacuum filtration.

#### 2.2.1. Synthesis of hexyl 4-methylbenzene-sulfonate (S1P1)

The amounts used in the reaction were: K<sub>2</sub>CO<sub>3</sub> (0.8804 g, 6.370 mmol), TsCl (0.5696 g, 2.988 mmol), 1-hexanol (0.1790 g, 1.751 mmol), KOH (0.5400 g, 9.624 mmol). Colorless oil; yield 20.99%; R<sub>f</sub> value: 0.60 (100% DCM); IR ( $\nu_{\text{max}}$ ) cm<sup>-1</sup>: 2957.85-2863.13 (C-H<sub>str</sub>), 1299.75 (S=O<sub>str</sub>); MF: C<sub>13</sub>H<sub>20</sub>O<sub>3</sub>S (MW: 256.36 g/mol); MS-ESI [M+Na]<sup>+</sup>: 279.1 m/z.



### 2.2.2. Synthesis of decyl 4-methylbenzene-sulfonate (S1P3)

The amounts used in the reaction were:  $K_2CO_3$  (0.5516 g, 3.991 mmol), TsCl (0.3091 g, 1.621 mmol), 1-decanol (0.1654 g, 1.045 mmol), KOH (0.3775 g, 6.728 mmol). Colorless oil; yield 72.91%; Rf value: 0.61 (100% DCM); IR ( $\nu_{max}$ )  $cm^{-1}$ : 2960.23-2926.20 (C-H<sub>str</sub>), 1306.63-1291.43 (S=O<sub>str</sub>). MF:  $C_{17}H_{28}O_3S$  (MW: 312.47 g/mol); MS-ESI [M+Na]<sup>+</sup>: 335.2 m/z.

### 2.3. General Procedures for the Synthesis of 4-(alkyloxy)benzaldehydes

The alkyl tosylates were reacted with *p*-hydroxybenzaldehyde (PHB) following the procedures from Al-Ajely et al. (2008) and Nawale et al. (2012). In a 50-mL round-bottom flask, the corresponding alkyl tosylate together with 4-hydroxybenzaldehyde and  $K_2CO_3$  were mixed in 10 mL of dry acetone. The mixture was refluxed and stirred for 6-8 hours. After cooling, the mixture was transferred in a beaker with cold distilled water. The product was extracted with DCM. The organic layer was collected and dried with anhydrous  $CaCl_2$ . After filtration, the solvent was removed under vacuum. The crude product was then subjected to column chromatography for purification using DCM as solvent.

### 2.3.1. Synthesis of 4-hexyloxybenzaldehyde (S2P1)

The quantities used in the reaction were:  $K_2CO_3$  (0.3435 g, 2.485 mmol), PHB (0.1408 g, 1.153 mmol), 1-hexyl tosylate (S1P1 prepared in situ). Dark orange liquid; yield 19.82%; Rf value: 0.65 (100% DCM); IR ( $\nu_{max}$ )  $cm^{-1}$ : 2923.82-2852.93 (C-H<sub>str</sub>), 1265.19-1176.82 (C-O<sub>str</sub>), 1689.09 (s) (C=O<sub>str</sub>); MF:  $C_{13}H_{18}O_2$  (MW: 206.28 g/mol); MS-ESI [M+Na]<sup>+</sup>: 229.1 m/z.

### 2.3.2. Synthesis of 4-decyloxybenzaldehyde (S2P3)

The quantities used in the reaction were:  $K_2CO_3$  (0.5960 g, 4.312 mmol), PHB (0.3232 g, 2.647 mmol), 1-decyl tosylate (S1P3) (0.5832 g, 1.866 mmol). Dark orange liquid; yield 73.54%; Rf value: 0.68 (100% DCM); IR ( $\nu_{max}$ )  $cm^{-1}$ : 293.80-2853.11 (C-H<sub>str</sub>), 1257.82-1157.71 (C-O<sub>str</sub>), 1690.05 (s) C=O benzaldehyde; MF:  $C_{17}H_{26}O_2$  (MW: 262.39 g/mol); MS-ESI [M+H]<sup>+</sup>: 263.2 m/z.

### 2.4. General Procedures for the Synthesis of (Z)-5-(4-(alkyloxy)benzylidene)-thiazolidine-2,4-diones

The purified 4-(alkyloxy)benzaldehydes were reacted with thiazolidine-2,4-dione (TZD) using Knoevenagel condensation patterned from the work of Nawale & Dhake (2012). In a 50-mL round bottom flask, the corresponding *p*-(alkyloxy)benzaldehyde and TZD were suspended in 10-15 mL toluene. A catalytic amount of piperidine (not more than 0.2 mL) was dropped to the mixture and refluxed for 6-7 hours. The reaction mixture was cooled and poured on cold distilled water. Resulting product was extracted with toluene and was purified by column chromatography.

### 2.4.1. Synthesis of (Z)-5-(4-hexyloxybenzylidene)-thiazolidine-2,4-dione (S3P1)

The quantities used in the reaction were: TZD (0.0420g, 0.3586 mmol), 4-hexyloxybenzaldehyde (S2P1) (0.0625 g, 0.3030 mmol). Yield 82%; Rf value 0.78 (4:1 EtOAc:Hex); mp 132-136 °C; IR ( $\nu_{max}$ )  $cm^{-1}$ : 3037.15 (Ar-CH<sub>str</sub>), 2925.50-2855.32 (C-H<sub>str</sub>), 1737.45-1689.87 (C=O<sub>str</sub>); <sup>1</sup>H NMR (500 MHz, Methanol-d<sub>4</sub>)  $\delta$ :



7.75 (s, 1H), 7.51 (d,  $J=8.8$  Hz, 2H), 7.05 (d,  $J=8.8$  Hz, 2H), 3.98 (t,  $J=6.5$  Hz, 2H), 1.79 (p,  $J=20.0, 10.4, 5.2$  Hz, 2H), 1.50 (p,  $J=13.0, 7.4, 6.0, 3.4$  Hz, 2H), 1.44 – 1.25 (m, 4H), 0.92 (t, 3H) ppm. MF:  $C_{16}H_{19}NO_3S$  (MW: 305.39 g/mol); MS-ESI [M-H]: 304.1086 m/z.

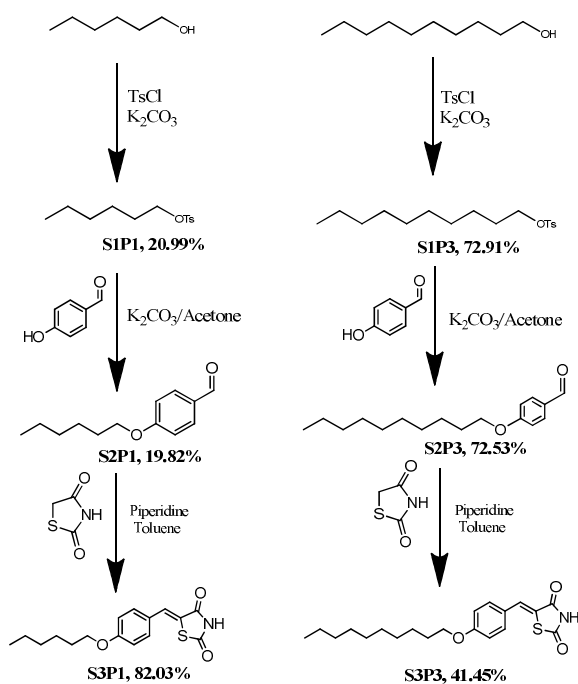
### 2.4.2 Synthesis of (Z)-5-(4-decyloxybenzylidene)-thiazolidine-2,4-dione (S3P3)

The quantities used in the reaction were: TZD (0.1351g, 1.153 mmol), 4-decyloxybenzaldehyde (S2P3) (0.2635 g, 1.004 mmol). Yield 41%; Rf value: 0.09 (4:1 Hex:EtOAc); mp 122-130 °C; IR ( $\nu_{max}$ )  $cm^{-1}$ : 3040.94 (Ar-CH<sub>str</sub>), 2924.49-2852.30 (C-H<sub>str</sub>), 1738.37-1687.63 (C=O<sub>str</sub>).  $^1H$  NMR (500 MHz, Methanol-d<sub>4</sub>)  $\delta$ : 7.75 (s, 1H), 7.51 (d, 2H), 7.05 (d, 2H), 4.05 (t,  $J=6.4$  Hz, 2H), 1.79 (p, 2H), 1.48 (p, 2H), 1.38 – 1.27 (m, 12H), 0.91 (t,  $J=6.7$  Hz, 3H) ppm. MF:  $C_{20}H_{27}NO_3S$  (MW: 361.50 g/mol); MS-ESI [M-H]: 360.1705 m/z.

## 3. RESULTS AND DISCUSSION

This study focuses in the synthesis and characterization of new TZD derivatives characterized by different lipophilic tails (Scheme 1).

Two alcohols (1-hexanol and 1-decanol) are converted into **S1P1** and **S1P3** via tosylation reaction by *p*-toluenesulfonyl chloride. *p*-hydroxybenzaldehyde is reacted with each of the tosylates to produce compounds **S2P1** and **S2P3** respectively. These are then incorporated with TZD to form the final products (**S3P1** and **S3P3**).



Scheme 1. Synthesis of thioazolidinedione derivatives

### 3.1 Synthesis of Alkyl Tosylates

Tosylation of alcohols were carried out to convert the alcohols into a tosyl ester which is a good leaving group. The solvent-free method was utilized in the synthesis. This method is simpler to carry out and is characterized by shorter reaction time. It also does not require a number of laboratory apparatus.

The addition of *t*-butanol near the end hastened the consumption of the excess TsCl by turning the *t*-butanol into isobutene (boiling point = -6.9°C) which is easily removed from the mixture because it is very volatile. The conversion of 1-decanol to its tosyl ester has higher yield compared to that of 1-hexanol.



### 3.2. Synthesis of 4-alkyloxybenzaldehydes

This second step involves the replacement of the *p*-toluenesulfonate group attached to the alkyl chain with *p*-hydroxybenzaldehyde via another S<sub>N</sub>2 reaction. The nucleophile in this step is the oxygen from the hydroxy group of PHB.

The most feasible reaction mechanism is that of a Williamson ether synthesis which starts with the formation of a nucleophile. K<sub>2</sub>CO<sub>3</sub>, as the base, abstracts the acidic proton from the phenolic hydroxide forming a resonance-stabilized 4-formyl phenolate. This nucleophile attacks the alkyl tosylate resulting to the substitution of the tosylate group.

### 3.3. Synthesis of (Z)-5-(4-(alkyloxy)-benzylidene)thiazolidine-2,4-diones

The last step involves a Knoevenagel condensation reaction of the 4-alkyloxybenzaldehyde and TZD. This condensation reaction starts with the attack of a nucleophile to the carbonyl carbon resulting to an alcohol. This alcohol consequently dehydrated to form an enone. The carbonyl group for this step comes from the aldehyde functional group of the 4-alkyloxybenzaldehydes. TZD is converted into a nucleophile by the weak base piperidine which abstracts a hydrogen from the lone sp<sup>3</sup> carbon of TZD.

The <sup>1</sup>H NMR spectrum shows that S3P1 was successfully synthesized. A singlet signal at 7.75 ppm (s, 1H) indicates a connection of the TZD to the aromatic ring. Moreover, a doublet signals at was seen at 7.51 ppm (d, J = 8.8 Hz, 2H) and 7.05 ppm (d, J = 8.8 Hz, 2H) corresponding to the hydrogens in the aromatic ring. A triplet signal at 3.98 ppm (t, J = 6.5 Hz, 2H) corresponds to the oxymethylene protons of the alkoxy chain. The <sup>1</sup>H NMR spectrum of S3P3 is consistent with that of S3P1 except for a higher integration of the protons in the alkyl chain which signifies a longer that a longer alkyl chain is attached.

## 4. CONCLUSIONS

In conclusion, two novel derivatives of 1,3-thiazolidine-2,4-dione (**S3P1** and **S3P2**) with alkyl chain moieties were successfully obtained in 3 steps. TZD is a known pharmacophore possessing interesting biological activities such as anti-cancer and anti-diabetes thus, it is recommended that biological studies of the synthesized TZD derivatives be carried out.

## 5. ACKNOWLEDGMENTS

The group wishes to acknowledge the University Research Coordinating Office (URCO) of De La Salle University (Manila, Philippines) for funding this research.

## 6. REFERENCES (use APA style for citations)

- Kazemi, F., Massah, A., & Javaherian, M. (2007). Chemoselective and scalable preparation of alkyl tosylates under solvent-free conditions. *Tetrahedron*, *63*, 5083-5087. doi:10.1016/j.tet.2007.03.083
- Key findings 2014 | International Diabetes Federation*. (2014). Retrieved from <http://www.idf.org/diabetesatlas/updaup-2014>
- Jaworska, J., & Nikolova, N. (2004). *Review of methods for assessing the applicability domains of SARS and QSARS*. Retrieved from [https://url-ecvam.jrc.ec.europa.eu/laboratories-research/predictive\\_toxicology/informainfo-sources/qsar-document-area/applicability\\_domain4.pdf](https://url-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/informainfo-sources/qsar-document-area/applicability_domain4.pdf)
- Malik, S., Upadhyaya, P. K., & Miglani, S. (2011). Thiazolidinediones: A plethora of biological load. *International Journal of PharmTech Research*, *3*(1), 62-75. ISSN: 0974-4304
- Nawale, S., & Dhake, A. (2012). Synthesis and evaluation of novel



Presented at the DLSU Research Congress 2016  
De La Salle University, Manila, Philippines  
March 7-9, 2016

thiazolidinedione derivatives for  
antibacterial activity. *Der Pharma  
Chemica*, 4(6), 2270-2277. Retrieved from  
<http://derpharmachemica.com/archive.html>



Presented at the DLSU Research Congress 2016  
De La Salle University, Manila, Philippines  
March 7-9, 2016