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Synthesis and Characterization of 5-pentadecyl-2.4-thiazolidinedione and 4-4'-[ethane-1,2-diylbis(oxy)]dibenzonitrile

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Abstract: The promising activity of thiazolidinediones has made it an attractive molecular feature in the development of new derivatives aimed to exhibit pharmacological significance. Thiazolidinedione-derived medicines are highly potent drugs for the treatment of diabetes mellitus type II (T2DM); it is known for its remarkable anti-hyperglycemic and insulin sensitizing property. Research shows that modification of the substituents on the thiazolidine-2,4-dione (TZD) moiety may lead to a plethora of beneficial biological activities. In this study, a derivative of TZD, 5-pentadecylthiazolidine-2,4-dione, containing a 15-carbon alkyl chain was prepared. The preparation involves the bimolecular nucleophilic substitution (S_N2) reaction of thiazolidine-2,4-dione and pentadecyl bromide with piperidine base and tetrahydrofuran as solvent. The product was obtained as white powder with a melting point of 54-55°C in 9.8 % yield. The compound will hopefully show greater potency and less adverse side effects relative to the anti-T2DM drugs present in the market. The compound was characterized using thin layer chromatography, melting point determination, and mass spectrometry.

Key Words: Thiazolidinedione, diabetes, anti-hyperglycemic; nucleophilic substitution

1. INTRODUCTION

Diabetes mellitus is a chronic disease that is caused either by an absolute deficiency in insulin secretion (type 1 diabetes mellitus) or by an endorgan insulin resistance (type 2 diabetes mellitus).Worldwide, it is estimated that 346 million people suffer of diabetes mellitus and among all, almost 90% are diagnosed with type 2 diabetes mellitus (T2DM) according to the World Health Organization. The authors (Lemke, Williams,Roche & Zito, 2008) found that type 2 diabetes mellitus is a metabolic disorder that can be caused by obesity and physical inactivity and is characterized by hyperglycaemia and hyperinsulinemia that may result in the development of serious of cardiovascular diseases and complications in the kidneys (nephropathy), nerves (neuropathy).

The treatment includes change in diet, insulin therapy and oral medication. Thiazolidine-2,4-dione (TZD) is a heterocyclic ring system with multifarious pharmacological applications. Thiazolidine-2,4-diones have been reported to be antiinflammatory, anti-cancer, anti-arthritics, antimicrobial and anti-hyperglycaemic.

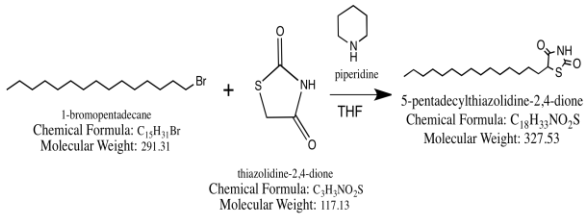
Thiazolidinediones are highly regarded for their anti-hyperglycaemic property. Among all diabetes drugs, only TZD derived drugs have insulin-sensitizing

properties and are efficient in controlling T2DM (Vora & Romaa, 2013). The representative derivatives of this class of therapeutic agents available in the market include troglitazone, rosiglitazone and pioglitazone. Thiazolidindiones exert their insulin sensitizing effect by binding to the transcription factor nuclear receptors peroxisome proliferator activated receptor γ (PPARγ), activating different genes that contribute to the increase in insulin sensitivity. Several structurally modified TZD analogues have been prepared and have shown potency similar to that of the T2DM drugs present in the market.

The versatile characteristic of the TZD moiety enable the synthesis of derivatives with varying structure-activity relationships (Yu,Ikeda, Oi & Sohda, 1991) (Imran, Ilyas, Babar,Khan & Khan, 2007) . In view of the multitude of pharmaceutical applications of thiazolidinediones, these observations prompted us to synthesize thiazolidinedione derivatives. These analogues may show greater potency in the treatment of T2DM or even to other various disorders. Furthermore, the new derivatives may also exhibit lesser side effects compared to the present marketed T2DM drugs. The synthesis of 5-pentadecyl-thiazolidine-2,4-dione involved the attachment of a 15-carbon long alkyl chain to the TZD moiety. The long alkyl chain will make the derivative more hydrophobic providing a better interaction with the lipid bilayer of the cell wall enabling the passage of the molecule across the cell membrane much faster. It is interesting to see whether this will greatly affect its potency compared to that with only one.

2. RESULTS AND DISCUSSION

Synthesis and Characterization of 5-pentadecyl-thiazolidine-2,4-dione



Scheme 1: Overview of the synthesis of 5-pentadecyl-thiazolidine-2,4-dione

The progress of the reaction was observed through TLC monitoring (solvent system: 75:25, DCM/Hexane). The TLC profile after 12hours of reflux revealed 4 spots: the highly non-polar 1-bromopentadecane (Rf=0.844), the assumed product (Rf=0.578) the unknown third spot (Rf=0.219), and fourth spot(Rf=0) dragging upwards from thiazolidine-2,4-dione and piperidine. After another 15 hours of reflux, the
TLC profile revealed the same spots (and same Rf values) but with the size of the spots of 1-bromopentadecane and the assumed product visibly decreased and increased, respectively. Reflux was decided to be continued for another 9 hours. At the 36th hour of reflux, with the same spots at the same Rf values, the increase in size of the assumed product was no longer as significant as it was at the 27th hour hence it was decided to stop the reflux. With the same favorable TLC profile, the product mixture was subjected to column chromatography for the purification of the mixture components. After the column chromatography of the crude product, the purified product obtained was white powdery crystals in 9.8 % yield with an Rf value of 0.633 using 75:25, DCM/Hexane as solvent system. It gave a sharp melting point at 54-55°C indicating a pure product. Mass spectrometry data showed the synthesis of the target compound with the molecular formula of $C_{18}H_{33}NO_2S$. Electrospray Ionization mass spectrometry gave a pseudomolecular ion peak

at [M-H] 326.2 while GC-MS gave an MS/EI (m/z) of 326.8.

Table 1. *Physical Properties of 5-pentadecyl-2,4-thiazolidinedione*

Physical Properties	Results
Description of the compound	*White Powdery Crystals*
Rf Value	*0.633 DCM:Hexane (75:25)*
Melting Point	*54-55°C*
% Yield	*9.8%*
MS/ESI (m/z)	*[M-H]- :326.2*
MS/EI (m/z)	*326. 8053*

3. METHODOLOGY

Synthesis of 5-pentadecyl-thiazolidine-2,4-dione

THF (3ml) was added to thiazolidine-2,4-dione (253mg, 2.160mmol) in a round bottom flask and was stirred for 20min. Piperidine (0.23ml, 2.313mmol) were added slowly to the solution then stirred for 20mins. 1-Bromopentadecane (0.550ml, 1.907mmol) were then added to the solution. The solution was stirred for 1hour and refluxed for 2 hours before leaving to stir overnight. The solution was refluxed for a total of 36 hours. Ice was added to the solution to obtain yellow-orange solids. The
solids were filtered using diethylether. The filtrate
collected was boiled off and was subjected to column chromatography with 100% Hexane, 75:25 Hexane/DCM, 50:50 Hexane/DCM, and 100%DCM as eluting solvents to obtain the target compound. The product generated white powdery crystals (61.21mg, 9.8%); R_f value: *0.633* (75% CH_2Cl_2:25% C_6H_{14}); MP: 54-55 ^oC; MS/ESI(m/z): $[M-H]^-$ *326.2*; MF: $C_{18}H_{33}NO_2S$ [MM: *326. 8053*]

4. CONCLUSION

The thiazolidinedione derivative with a 15-carbon alkyl chain attached to the TZD moiety, 5-pentadecyl-thiazolidine-2,4-dione was synthesized and characterized. The preparation of 5-pentadecylthiazolidine-2,4-dione involves the S_N2 reaction of thiazolidine-2,4-dione and 1-bromopentadecane with piperidine base and tetrahydrofuran as solvent. It was obtained as white powdery crystals in 9.8% yield with a melting point of 54-55°C. The product was characterized using Mass Spectrometry.

5. REFERENCES

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