Acta Pharmaceutica Turcica
XXXIX (1) 33-37 (1997)

SYNTHESIS AND ANTIHYPERGLYCEMIC ACTIVITY OF NOVEL FLAVONYL 2,4-THIAZOLIDINEDIONES

YENİ FLAVONİL-2,4-TİAZOLİDİNDİONLARIN SENTEZİ VE ANTİHİPERGLİSEMİK ETKİLERİ

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In this study, novel flavonyl-2,4-thiazolidinediones were synthesized. These compounds were obtained by linking the flavone and the 2,4-thiazolidinedione rings up using a methylene and/or a methyne groups. Their chemical structures have been elucidated by IR, ^{1}H-NMR, Mass spectra and elementary analysis. Furthermore, the synthesized compounds are under investigation for antihyperglycemic activity.

Bu çalışmada, yeni flavonil-2,4-tiazolidindionlar sentezlenmiştir. Bu bileşikler, flavon ve 2,4-tiazolidindion halkalarının metilen ve/veya metin grupları kullanılarak birleştirilmesi ile elde edilmişlerdir. Bileşiklerin kimyasal yapıları IR, ^{1}H-NMR, Mass ve elemanter analiz bulguları ile aydınlatılmıştır. Ayrıca, sentez edilen bileşikler antihiperglisemik etki yönünden incelenmektedir.

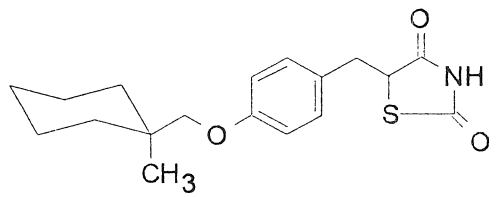
Keywords : *Antihyperglycemic activity; Flavonyl-2,4-thiazolidinediones ; 2,4-thiazolidinediones*

Anahtar kelimeler: *Antihiperglisemik aktivite; Flavonil-2,4-tiazolidindionlar; 2,4-tiazolidindionlar*

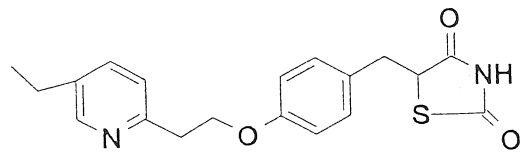
Introduction

Diabetes is a chronic disease affecting 5% of the population of the industrialized world. Most of the diabetes are type II or non-insulin dependent diabetes mellitus (NIDDM) (1). NIDDM is a complex chronic metabolic disorder characterized by insulin resistance in the liver and peripheral tissues (1-7). Advences in the understanding of glucose metabolism and insulin action have led to recent efforts to develop new oral agents for the treatment of NIDDM. Therapeutic agents currently in development act *via* a variety of different mechanisms to lower glucose levels including inhibition of fatty acid oxidation, α-glucosidase inhibition, antagonism of α_2-adrenoceptors, β_3-adrenergic receptor agonism and inhibition of gluconeogenesis (1).

One of the most promising approaches for control of NIDDM is through potentiation of peripheral insulin action. The prototypical agent in this class namely ciglitazone (**I**), is a p-alkoxybenzyl-substituted thiazolidinedione (1-3,7). Structure-activity-relationship studies have led to the discovery of a number of agents which have entered clinical development, including pioglitazone (**II**), englitazone (**III**) and troglitazone (**IV**) (1,2,7).



I



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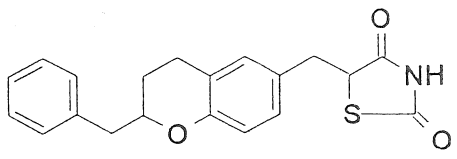

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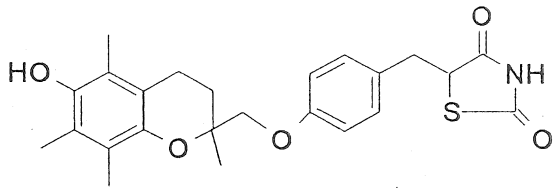
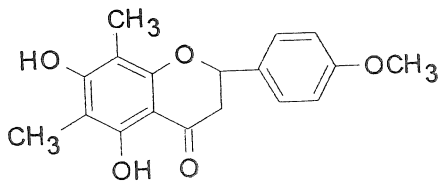
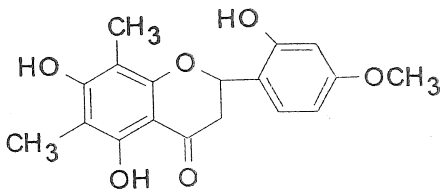


IV

On the other hand, C-methyl flavanone drivatives such as matteucinol (**V**) and 2'-hydroxy-matteucinol (**VI**) were found to show very strong hypoglycemic activity in streptozotocin-induced diabetic rats(8).

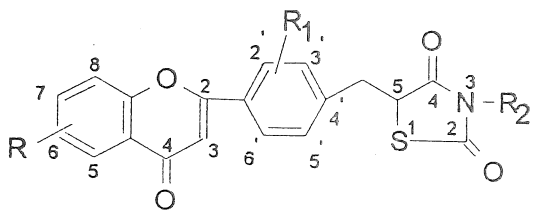


V



VI

In this study, novel flavonyl 2,4- thiazolidinediones were synthesized. General formula of flavonyl-2,4-thiazolidinediones(**VII**) that were planned to be synthesized is given below. Their chemical structures have been proven by IR, ^{1}H-NMR, Mass spectra and elementary analysis. Furthermore, the synthesized compounds are under investigation for antihyperglycemic activity.



VII

Materials and Methods

Melting points were determined with a Buchi SMP 20 capillary melting point apparatus and uncorrected. IR spectra were recorded on a Unicam SP 1025 Infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a Bruker AC300 MHz instrument using TMS internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. Mass spectra were recorded on a VG analytical 70-250 S spectrometer with EI methods. Column chromatography was carried out using flash method and Merck Silica gel 60 (230-400 mesh ASTM). All the chemical reagents used in the synthesis were purchased from E.Merck (Darmstadt, FRG) and Aldrich (Milwaukee, WI, USA).

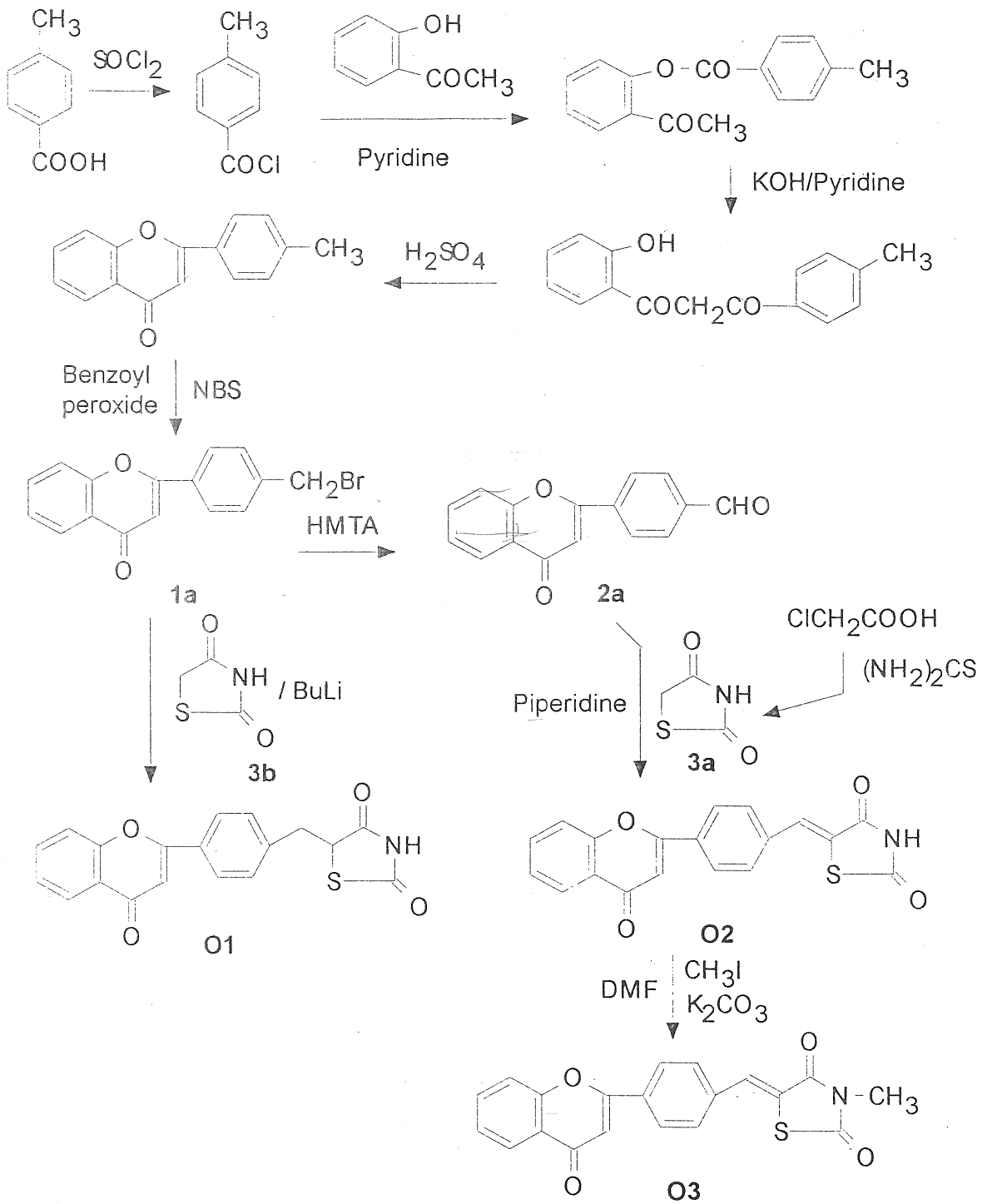
I.To reach the molecules that were planned to be synthesized, the starting materials were synthesized as given in the literatures (Scheme 1).

I.1-Synthesis of 4'-Carboxaldehyde flavone(**2a**):

This product was obtained by convertion to carboxaldehyde from bromomethyl-flavone group by using hexamethylenetetramine (9).

I.2-Synthesis of 2,4-thiazolidinedione (**3a**)

It was synthesized by treating $ClCH_2COOH$ with thiourea (10).



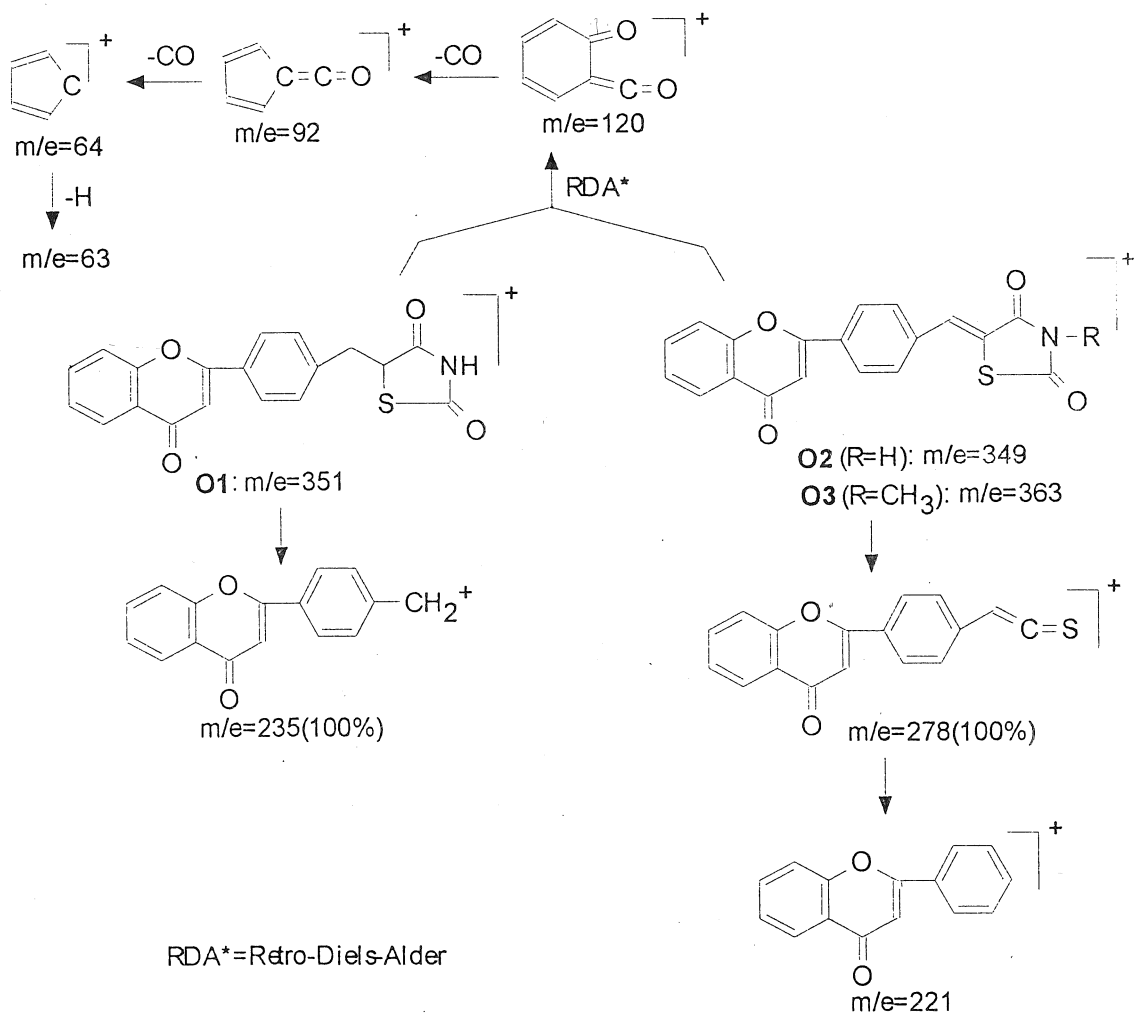
Scheme 1. Synthesis of the compounds

II- Synthesis of 5-[4'-(4H-4-oxo-1-benzopyran-2-yl) benzyl]-2,4-thiazolidinedione (**O1**):

To a stirred solution of **3a** (0.377 g, 3.2 mmol) in THF (50 ml) at -78°C under argon was added n-buthyllithium (0.59 ml, 6.4 mmol) portionwise over 15 min and then warmed to 0°C for 30 min to complete the anion formation. Upon recooling to -78°C, **1a** (1.0g, 3.2 mmol) was added as a solid, all at once. After 30 min the solution was allowed to warm to 25°C. After 1.5 h the reaction mixture was treated with aqueous H_2SO_4. The aqueous phase was washed three times with $CHCl_3$, and the combined organic extracts were dried over Na_2SO_4, and concentrated to give crude product, which was purified by column chromatography (0.15 g, 13.3%): M.p. 194-8°C; IR (cm^{-1}): 1655 (γ-benzopyran C=O); 1735, 1780 (thiazolidinedione ring C=O); ^{1}H-NMR (DMSO-d_6), (δppm): 3.2-3.28 (dd,2H,CH_2), 4.95 (dd,1H,CH), 7.0 (s,1H,3-H), 7.45 (d,2H,3',5'-H), 7.4-7.8 (m,3H,6-8-H), 8.0 (dd,1H,5-H), 8.05 (d,2H,2',6'-H); Mass EI 70eV: m/e351 (M^+), 235 (100%), 120, 92,63. Anal. for $C_{19}H_{13}NO_4S.H_2O$ Cald. C:61.78, H:4.09, N:3.79, Found. C:62.34, H:3.98, N:3.25.

III- Synthesis of 5-[4'-(4H-4-oxo-1-benzopyran-2-yl) benzyliden]-2,4-thiazolidinedione(**O2**):

A mixture of **2a** (0.5g, 2mmol), **3a** (0.47 g, 4 mmol), piperidine(0.2ml), and EtOH(10 ml) was refluxed16h. After cooling, the precipitated crystals were collected by filtration to give the title compound (0.4g, 57.3%): M.p. 305-7°C; IR (cm^{-1}) : 1655 (γ-benzopyran C=O); 1735, 1780 (thiazolidinedione ring C=O); ^{1}H-NMR (DMSO-d_6), (δppm): 7.1 (s, 1H, 3-H), 7.45



Scheme 2. Mass fragmentation of the compounds

(ddd,1H,6-H), 7.75(d,2H,3',5'-H), 7.7-7.8(m,2H,7,8-H), 7.8(s,1H,=CH), 8.05(d,1H,5-H), 8.2(d,2H,2',6'-H); Mass, EI 70eV:m/e349(M^+), 278(100%), 221, 120, 92, 63. Anal. for $C_{19}H_{11}NO_4S.H_2O$ Calcd. C:62.12, H:3.56, N:3.81, Found. C:62.35, H:3.22, N:3.93

IV- Synthesis of 3-methyl, 5-[4'-(4H-4-oxo-1-benzopyran-2-yl)-benzyliden]-2,4-thiazolidinedione (**O3**):

A mixture of **O2** (0.1g, 0.29mmol), Na_2CO_3 (0.03g), CH_3I (0.04 ml) and DMF (5 ml) was stirred at 40°C for 3h,diluted with H_2O, filtered, and crystalized EtOH (0.1g, 96%):M.p. 250°C; IR (cm^{-1}):1680 (γ-benzopyran C=O); 1720, 1780 (thiazolidinedione ring C=O); ^{1}H-NMR (DMSO-d_6), (δppm): 3.1 (s,3H,CH_3), 7.15(s, 1H, 3-H), 7.5 (ddd, 1H, 6-H), 7.8 (s, 1H, =CH), 7.8-8.3 (m, 7H, 5, 7, 8&2', 3', 5', 6'-H); Mass, EI 70eV:m/e363(M^+), 278 (100%), 221, 120, 92, 63. Anal. for $C_{20}H_{13}NO_4S.1/2H_2O$ Calcd. C:64.50, H:3.78, N:3.76, Found. C:63.86, H:3.28, N:3.78

Results and Discussion

For the synthesis of novel 2,4-thiazolidinedione derivatives at the first step 4'-methyl flavone was obtained by the general method which is known as Baker-Venkataraman. Methyl group of the flavone was converted to bromomethyl and then this group was changed to the carboxaldehyde. Methylenyl group linker between the flavone and 2,4-thiazolidinedione derivatives were synthesized by Knoevenagel condensation of the 4'-carboxaldehyde flavone. Piperidine was generally used as the base in this condensation. A methyne group linker between the flavone and the 2,4-thiazolidinedione rings were synthesized by dilithio-2,4-thiazolidinedione(**3b**) with appropriate's bromide.

The formula, melting points, % yields of the compounds are showed under the synthesis methods for compounds. All spectral data were in accordance with assumed structures. The IR spectra of the compounds showed γ-benzypran C=O stretching bonds at 1655-1680 cm^{-1} and thiazolidinedione ring C=O stretching bonds at 1720-1780 cm^{-1}. In ^{1}H-NMR spectra C-3,C-5, C-6, C-7 and C-8 protons of 4H-benzopyran ring and flavone B ring protons were seen between 7.0-8.3 ppm. In mass spectra, all the compounds have molecular ion peaks (M^+) (Sheme 2).

The synthesized compounds are subjected to investigation for antihyperglycemic activity. According to antihyperglycemic activity results, more flavonyl-2,4-thiazolidinedione type compounds will be synthesized as described in introduction part (see **VII**).

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Accepted : 07.05.1996