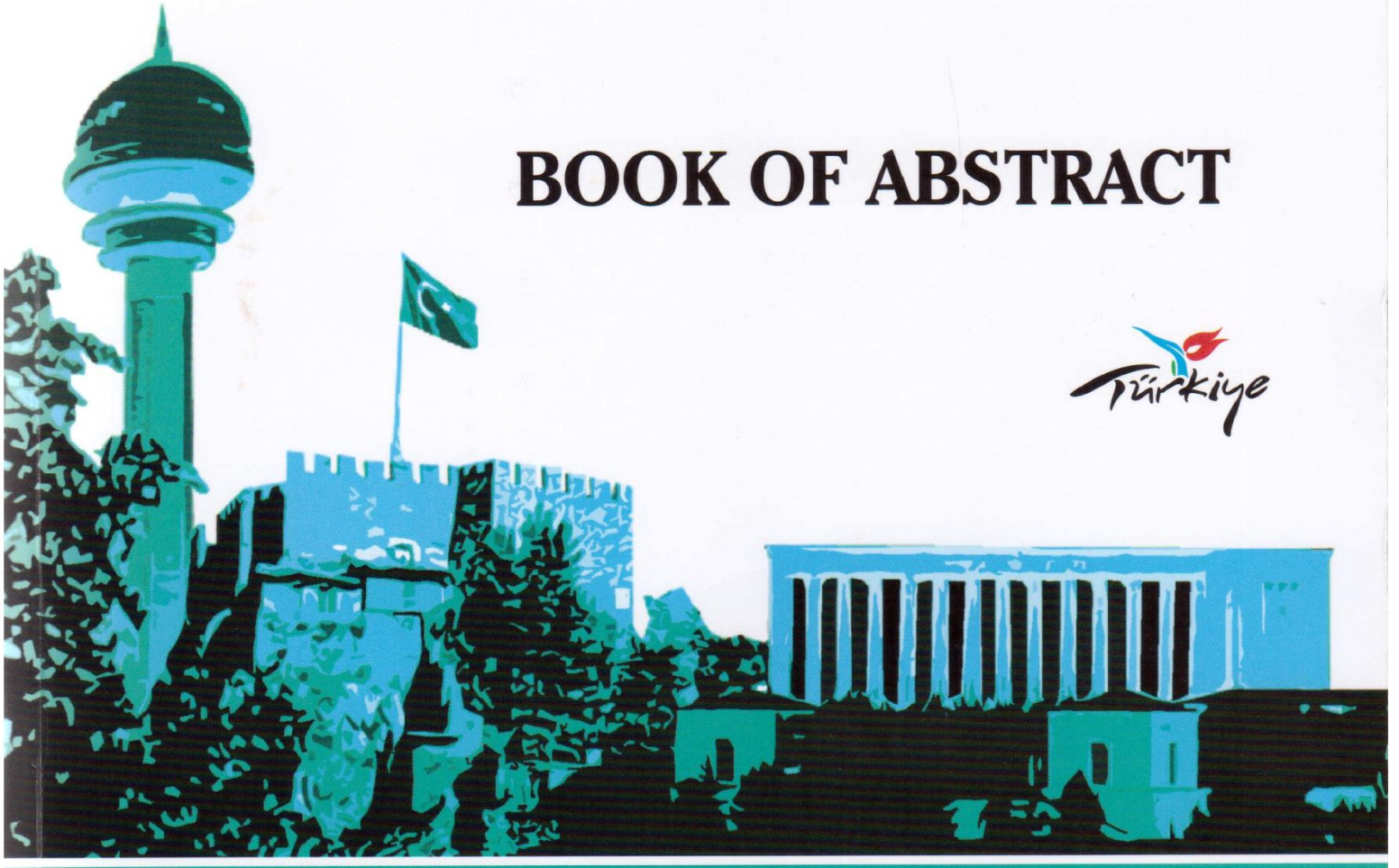
ANKARA UNIVERSITY
FACULTY OF PHARMACY

ISOPS 11th International SYMPOSIUM ON PHARMACEUTICAL SCIENCES

BOOK OF ABSTRACT



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KÜLTÜR VE TURİZM BAKANLIĞI

TUBİTAK

JUNE 09-12, 2015
ANKARA, TURKEY

Efficacy Of Morpholino-Substituted Chalcone Derivative Compounds. TPE 2011/05601, 2011

P-177: NOVEL 6-SUBSTITUTED-3-(2*H*)-PYRIDAZINONE-2-ACETYL-2-(2,4-DISUBSTITUTEDBENZAL) HYDRAZONE DERIVATIVES: SYNTHESIS AND STRUCTURE ELUCIDATION

A.B. Özçelik[1], S. Utku[2], Ö. Güler[1,3], M. Uysal[1]

[1]Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara, TURKEY
[2]Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Mersin, TURKEY
[3]Dicle University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Diyarbakır, TURKEY

INTRODUCTION

In recent years, a great deal of work have been directed to the synthesis of 3(2*H*)-pyridazinones derivatives. These nitrogen heterocyclic compounds are biological importance and therefore, design and strategy for their synthesis is important in medicinal chemistry [1]. Pyridazinone derivatives have been reported to exhibited wide range of pharmacological activities such as antidepressant, antihypertensive, antithrombotic, anticonvulsant, cardiotonic, antibacterial, diuretic, anti-HIV, aldose reductase inhibitors, anti-inflammatory, anticancer [2].

Here we report a convenient and versatile synthetic approach to novel 6-Substituted-3-(2*H*)-pyridazinone-2-acetyl-2-(2,4-disubstitutedbenzal) hydrazone derivatives.

MATERIALS AND METHODS

The fine chemicals and all solvents used in this study were purchased from Merck and Aldrich Chemical Co. Melting points of the compounds were determined on Electrothermal 9200 melting points apparatus and the values given are uncorrected. FTIR spectra were recorded on an ATR apparatus on a Perkin Elmer Spectrum 100 Fourier Transform spectrophotometer. Elemental analyses were performed with Costech Combustion System CHNS-O analyzer and ^{1}HNMR spectra were recorded in DMSO-d_6 on a Bruker AV400 MHz FT NMR spectrometer.

The synthesis of **I, II, III** has already been reported in the literature [3]. Ethyl 6-substituted-3(2*H*)-pyridazinone-2-ylacetate **IV** derivatives were obtained by the reaction of **III** with ethyl bromoacetate in the presence of K_2CO_3 in acetone. 6-Substituted-3(2H)-pyridazinone-2-yl acetohydrazide derivatives **V** were synthesized by the condensation reaction of III derivatives with hydrazine hydrate (99%). Synthesis of title compounds **VI** were performed reaction of 6-substituted-3(2*H*)-pyridazinone-2-yl acetohydrazide derivatives **V** with 2,4-disubstituted benzaldehydes.

RESULTS AND DISCUSSION

Seventeen new final compounds **IV**, **V** and **VIa-VIo** were synthesized according to the procedures depicted in Figure. The elemental analysis data for each compound were in good agreement with the empirical formula proposed. In the IR spectra of newly synthesized compounds **Va-o** exhibited characteristic υ (C=O) bands at 1703-1707 and 1662-1668 cm^{-1} for acetyl side chain and pyridazinone ring respectively. The υ (N—H) stretching bands centered at 3212-3218 cm^{-1}.

The ^{1}H NMR spectra of all complexes were consistent with their corresponding protons as chemical shift values and the number of hydrogen. Synthesized compounds **IV**, **V** and **VIa-VIo** derivatives were reported first time in this study.

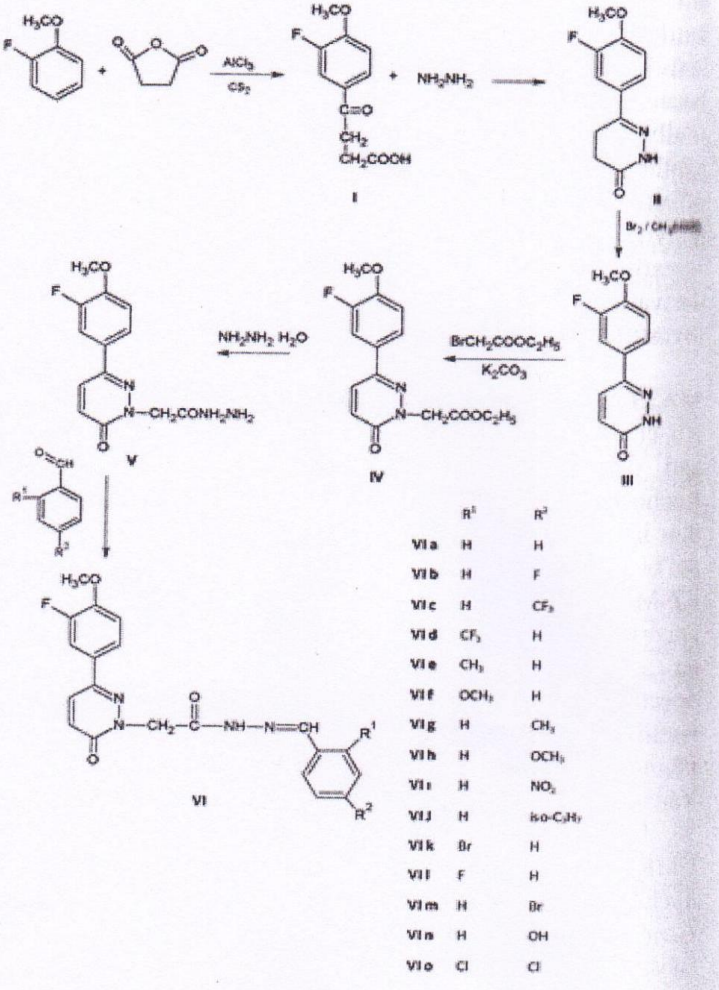

Fig. 1. Synthetic route of the synthesized compounds

CONCLUSIONS

We report here in the synthesis of a series of novel **IV**, **V**, **VIa-o** derivatives. All synthesized compounds have been structurally elucidated and the basis of spectroscopic means.

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2. Xing, W.; Ai, J.; Jin, S.; Shi, Z.; Peng, X.; Wang, L.; Ji, Y.; Geng, M.; Hu, Y., Enhancing the cellular anti-proliferation activity of pyridazinones as c-met inhibitors using docking analysis. *Eur J Med Chem* **2015**, 95, 302-312.
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P-178: SYNTHESIS OF AMINO ACID ESTER DERIVATIVES OF ACETYLSALICYLIC ACID

B. Eymur, G. Taskor, N. Saygılı

Hacettepe University, Faculty of Pharmacy, Department of Basic Pharmaceutical Sciences, Ankara, TURKEY

Synthesis of new acetylsalicylic acid derivatives is significant due to their activities in biological systems with reduced side effects. Acetylsalicylic acid chloride was reacted with different aminoacid esters to afford aspirin derivatives. The new acetylsalicylic acid derivatives were characterized by ^{1}H NMR, ^{13}C NMR and MS.

INTRODUCTION

Aspirin (1), 2-acetoxybenzoic acid, is a most widely used safe non-steroidal anti-inflammatory drug (NSAID). It has the ability to reduce pain (an analgesic) and to reduce fever (an antipyretic), to reduce swelling and soreness (an anti-inflammatory agent) [1]. It may be used to prevent stroke, heart attack, and cancer [2].

Long term use of aspirin is a concern because of its side effects. Some of the undesirable side effects of aspirin result from acidity to induce gastric or intestinal ulceration [2]. It can be avoided by decreasing the acidity. In the present study, it was planned to synthesize derivatives of aspirin in order to reduce its side effects and to make it more biocompatible as a drug.

MATERIALS AND METHODS

All reagents were of commercial quality and reagent quality solvents were used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400MHz FT-NMR spectrometer in $CDCl_3$ solutions using TMS as the internal standard. The purity of the compounds was assessed by TLC on silica gel 60 F_{254}. Column chromatography was conducted on silica gel 60 (mesh size 0.063–0.200mm). Mass spectra (ESI-TOF-MS) were recorded on Waters Synapt MS System mass spectrometer.

Procedure for the Preparation of Amino Acid Methyl Esters [3]: Thionyl chloride (1.8 mL, 25 mmol) was added dropwise to methanol (20 mL) at 0°C. Amino acid (10 mmol) was added and the mixture was stirred at room temperature for 100 h. The residue was evaporated *in vacuum*, dissolved in 20 ml of methanol and evaporated *in vacuum*. This was repeated for three times. Then the residue was dissolved in 20 ml of ether and evaporated *in vacuum*. This was repeated for three times. The residue was crystallized in ether to provide the title compounds as colourless powder.

Procedure for the Preparation of Acyl Chloride (2) [4]: Thionyl chloride (0.7 mL, 0.10 mol) was added to the stirring solution of aspirin (9 g, 0.05 mol) in dry CH_2Cl_2 (20 mL). The resulting mixture was heated at reflux until the disappearance of the carboxylic acid was fully completed (TLC; 2-8 h). After cooling, the mixture was concentrated on a rotary evaporator. The crude products were distilled under reduced pressure to yield the pure acid chloride.

Procedure for the Preparation of Aspirin Derivatives [5]: Amino acid ester (2.2 mmol) was dissolved and stirred in CH_2Cl_2 (15 mL), cooled to -5°C, and then treated with Et_3N (4.4 mmol). Acetylsalicylic acid chloride (2.0 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was stirred at room temperature for ~1 week. The crude product purified using column chromatography.

RESULTS AND DISCUSSION

The reaction of acetylsalicylic acid chloride with each aminoacid methyl ester, in the presence of the non-nucleophilic base triethylamine, gave the corresponding aminoacid ester derivatives of aspirin. The products formed were confirmed by ^{1}H NMR, ^{13}C NMR and MS.

Synthesis of Dimethyl 2-(o-acetoxybenzamido) pentanedioate: Acetylsalicylic acid chloride (2 mmol, 397 mg), dimethyl 2-aminopentanedioate (2.2 mmol, 385 mg) Et_3N (0.6 mL, 4.4 mmol) in CH_2Cl_2; eluent EtOAc–hexane 1:1 (v/v) gave compound **3** as a yellow viscous liquid (485 mg, 72 % yield). ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, J = 8.0 Hz, ArH_a), 7.41 (t, 1H, J = 8.0 Hz, ArH_c), 7.23 (t, 1H, J = 8.0 Hz, ArH_b), 7.06 (d, 1H, J = 8.0 Hz, ArH_d), 6.56 (s, 1H, N*H*), 4.77 (m, 1H, 2-*H*), 3.70 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 2.38 (t, 2H, J = 8.0 Hz, 4-*H*), 2.33 (s, 3H, CH_3), 2.24 (m, 2H, 3-*H*); ^{13}C-NMR ($CDCl_3$) δ 172.16, 168.67, 164.98, 148.17, 132.18, 130.34, 126.85, 126.24, 123.37, 52.64, 51.82, 29.68, 27.63, 21.07. HRMS (EI) calcd for $C_{16}H_{19}NO_7$ (M^+) 338.1246, found 338.1240.

CONCLUSIONS

Clinical based study showed that the patients who use NSAIDs on a chronic basis have more risk for gastric events compared to the general population of non-users. This study describes the synthesis of new aspirin derivatives as compounds to decrease or eliminate its side effects without changing its pharmacological