ANKARA UNIVERSITY
FACULTY OF PHARMACY

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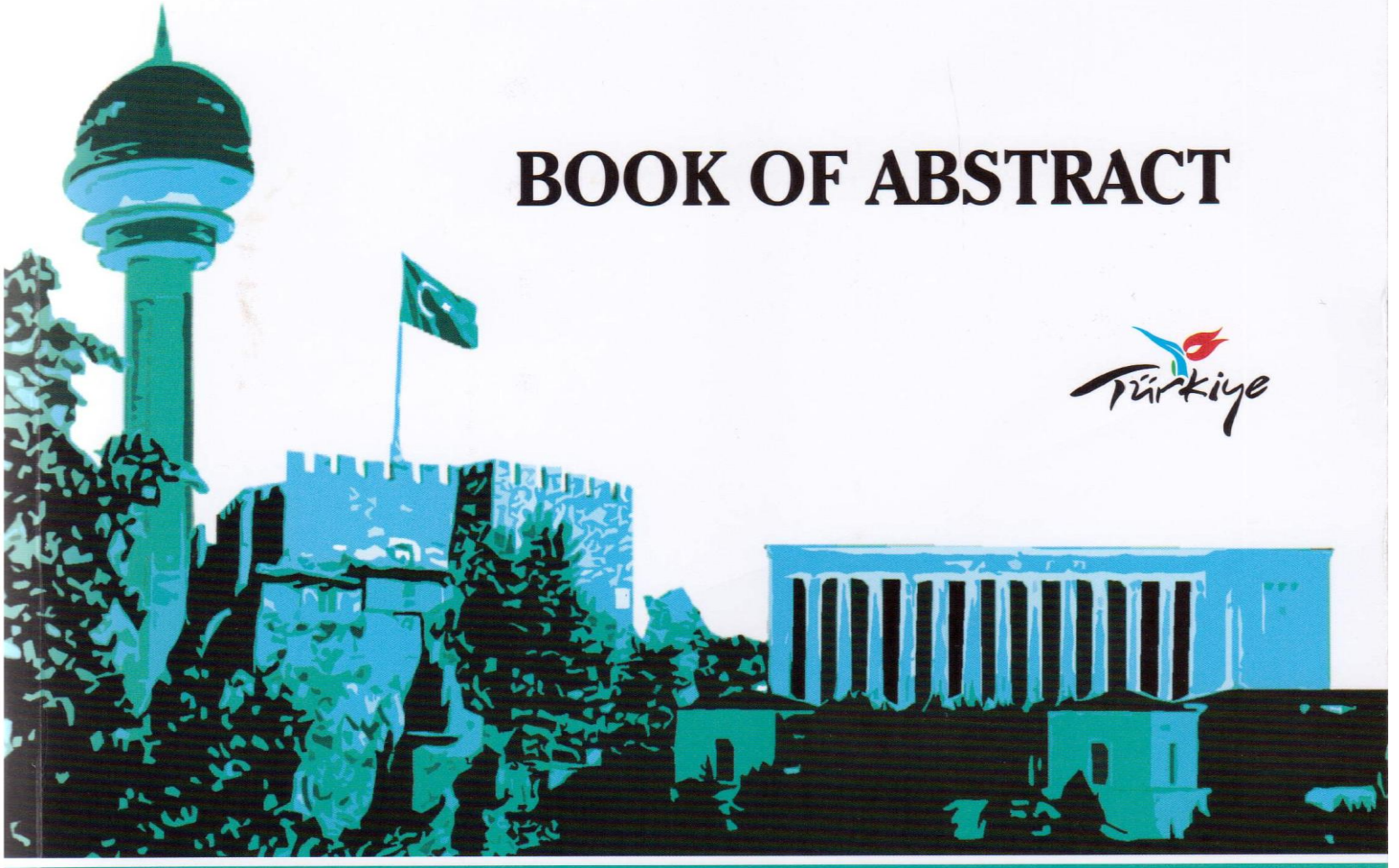
BOOK OF ABSTRACT



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TUBİTAK

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consistent with their corresponding protons as chemical shift values and the number of hydrogen. IR spectra of newly synthesized compounds **II** and **III** derivatives exhibited characteristic υ (C=O) bands at 1713-1715 and 1668-1674 cm^{-1} for acetyl side chain and pyridazinone ring respectively.

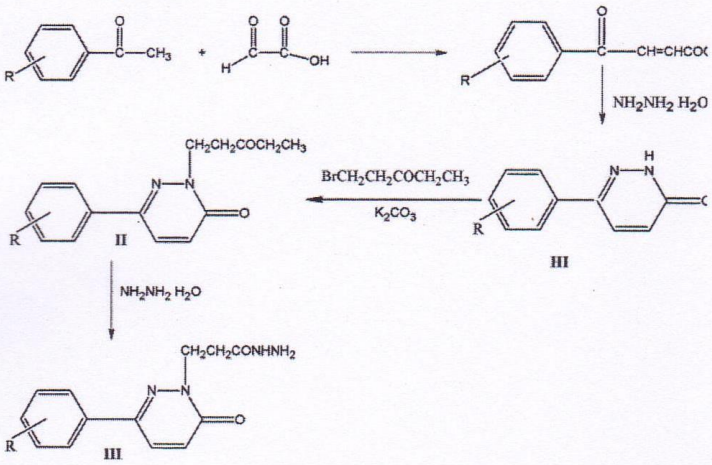

Fig. 1. Synthesis pathway of ethyl 6-substituted-3(2*H*)-pyridazinone-2-ylacetate **II** and 6-substituted-3(2*H*)-pyridazinone-2-yl acetohydrazide derivatives **III**

CONCLUSIONS

All of the **II** and **III** derivatives were synthesized for the first time in this study. Chemical structures of synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-NMR and Mass spectral data. Detailed anticancer activity of synthesized compound will be investigated in our next study.

REFERENCES

1. Dal Piaz, V.; Giovannoni, M. P.; Ciciani, G.; Becherucci, C.; Parente, L., *Pharmacological Res*. **1994**, *29*, 367-372.
2. Franzen, K.; Saveman, B.; Blomqvist K. *Eur. J. Cardiovasc Nurs*, **2007**, *6*, 112-120.
3. Nieminen, M. S.; Cleland, J.G.F.; Eha, J.; Belenkov, Y.; Kivikko, M.; Poder, P.; Sarapohja, T., *Eur J Heart Failure*, **2008**, *10*, 1246-1254.
4. Sotelo, E.; Fraiz, N.; Yanez, M.; Terrades, V.; Laguna, R.; Cano, E., *Bioorg Med Chem* 2002, *10*, 2873-2882.
5. Schudt, C.; Winder, S.; Müller, B.; Ukena, D., *Biochem. Pharmacol.* **1991**, *42*, 153-162.

P-222: SYNTHESIS OF 6-SUBSTITUTED-3(2H)-PYRIDAZINONE-2-ACETYL-2-(SUBSTITUTED/NONSUBSTITUTED BENZAL)HYDRAZONE DERIVATIVES

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INTRODUCTION

In recent years, a great deal of work have been directed to the organic synthesis of 3(2*H*)-pyridazinones derivatives. Pyridazinone derivatives have established a variety of pharmacological activities most of them are related to cardiovascular effects. In this field a number of compounds such as zardaverine, bemoradan, indolindan, pimobendan are few examples of pyridazinones that are active as cardio tonic agents/platelet [1,2]. During our literature research, we observed that compounds synthesized in the recent studies possessed notable antidepressant, antihypertensive, antithrombotic, antifungal, antibacterial, analgesic anti-inflammatory, antiplatelet, anticancer, anti-HIV, vasodilator and antiasthmatic effects on cardiovascular system [3,4]. This study was an attempt together the different developments for synthesis and anticancer activities of pyridazinone derivatives.

MATERIALS AND METHODS

The fine chemicals and all solvents used in this study were purchased locally from E. Merck (Darmstadt, F. R. Germany) and Aldrich Chemical Co. (Steinheim, Germany). Melting points of the compounds were determined on Electrothermal 9200 melting points apparatus (Southent, Great Britain) and the values given are uncorrected. IR spectra were obtained using a Perkin Elmer Spectrum 400 FTIR/FTNIR spectrometer equipped with a Universal. Mass Spectrometer (high sensitivity orthogonal acceleration time-of-flight instrument) operating in ESI method, also coupled to an AQUITY Ultra Performance Liquid Chromatography system. The ^{1}H-NMR of the compounds spectra were recorded on a Bruker Avonce 300 MHz UltrashieldTM NMR Spectrometer using tetramethylsilane as an internal standard.

New 6-substituted-3(2*H*)-pyridazinone-2-acetyl-3-(p-substituted/nonsubstituted benzal)hydrazone **IV** derivatives were synthesized according to Figure 1. Ethyl 6-substituted-3(2*H*)-pyridazinone-2-ylacetate **II** derivatives were obtained by the reaction of **I** with ethylbromoacetate in the presence of K_2CO_3 in acetone. 6-Substituted-3(2*H*)-pyridazinone-2-yl acetohydrazide derivatives **III** were synthesized by the condensation reaction of **II** derivatives with hydrazine hydrate. Synthesis of title compounds **IV** were performed reaction of 6-substituted-3(2*H*)-pyridazinone-2-yl acetohydrazide derivatives **III** with substituted/nonsubstituted benzaldehydes.

RESULTS AND DISCUSSION

We describe here the synthesis of new 6-substituted-3(2*H*)-pyridazinone-2acetyl-3-(p-

substituted/nonsubstituted benzal)hydrazone **IV** derivatives. The elemental analysis data for each compound were in good agreement with the empirical formula proposed. Chemical structures of synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-NMR and Mass spectral data

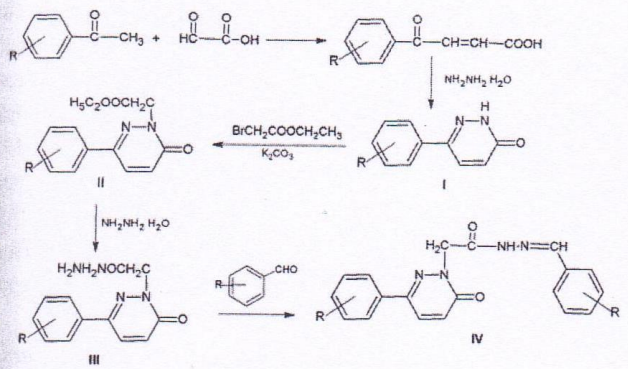

Fig. 1. Synthesis pathway of 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted benzal) hydrazone **IV** derivatives

CONCLUSIONS

All of the **IV** derivatives were synthesized for the first time in this study. Our aim was to establish more detailed structure-activity relationship in this series and evaluate the modification of the pharmacological profile induced by the substituents in the 6-position of the 3(2*H*)-pyridazinone derivatives. Detailed anticancer activity of synthesized compound will be investigated in our next study.

REFERENCES

1. Ovais, S.; Javed, K.; Yaseen, S.; Bashir, R.; Rathore, P.; Yaseen, R.; Hameed, AD.; Samim, M., Synthesis, antiproliferative and anti-inflammatory activities of some novel 6-aryl-2-(p-(methanesulfonyl)phenyl)4,5-dihydropyridazi-3(2H)-ones. *Eur J Med Chem* **2013**, *67*, 352-358.
2. Frolov, E.B.; Lakner, F.J.; Khvat, A.V.; Ivachtchenko, A.V., An efficient synthesis of novel 1,3-oxazolo[4,5-d]pyridazinones. *Tetrahedron Lett* **2004**, *45*, 4693-4696.
3. Humphries, P.S.; Oliver, R.M., Facile synthesis of 4,5-disubstituted-3(2H)-pyridazinones. *Tetrahedron Lett* **2009**, *50*, 2682-2684.
4. Rathish, I.G.; Javed, K.; Ahmad, S.; Bano, S.; Alam, M.S.; Akhter, M.; Pillai, K.K.; Ovais, S.; samim, M., Synthesis and evaluation of anticancer activity of some novel 6-aryl-2-(p-sulfamylphenyl)-pyridazin-3(2H)-ones. *Eur J Med Chem* **2012**, *49*, 304-309.

P-223: MICROWAVE-ASSISTED SYNTHESIS OF CONDENSED 1,4-DIHYDROPYRIDINE DERIVATIVES AS POTENTIAL CALCIUM CHANNEL MODULATORS

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This study reports the synthesis and calcium channel modulatory activity evaluation of 14 novel fused 1,4-dihydropyridine derivatives. The compounds were achieved by one-pot microwave-assisted reaction according to a modified Hantzsch synthesis. The structures of the compounds were confirmed by spectral methods and elemental analysis. To evaluate their relaxant activities, the maximum relaxant response (E_{max}) and pD_2 values of the compounds and nifedipine were determined on isolated rat aorta rings. The E_{max} values (a measure of efficacy) of five compounds have been found higher than that of nifedipine.

INTRODUCTION

Calcium channel blockers are the class of drugs that inhibit selectively the calcium influx through cell membranes. L-type channels are highly sensitive to 1,4-dihydropyridines (DHPs), which represent a well-known class of calcium antagonists. DHPs are clinically used as treatments for cardiovascular diseases particularly hypertension and angina [1]. Here, we described an efficient method based on microwave irradiation for fourteen novel DHP derivatives in which substituted cyclohexane rings are fused to the DHP ring, and we determined how different ester groups affect calcium channel block.

MATERIALS AND METHODS

The general procedure for the preparation the compounds was as follows: The mixture of 4,4-dimethyl-1,3-cyclohexanedione, chloro-substituted-salicylaldehyde, appropriate alkyl acetoacetate and ammonium acetate were heated under microwave irradiation in methanol.

The E_{max} and pD_2 values of the compounds were determined on isolated rat aorta rings.

RESULTS AND DISCUSSION

The obtained pharmacological results showed that all synthesized compounds are potent relaxing agents on isolated rat aorta smooth muscle due to blockade of calcium channels, similar to that of nifedipine. Given that the main difference between these compounds is