ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA

VOL. LXII, 19 SECTIO AA 2007

Synthesis of new derivatives of 2- and 3-benzo[b]furan carboxylic acids

J. Kossakowski, K. Ostrowska and M. Struga
Department of Medical Chemistry, Medical University of Warsaw, Oczki 3, 02-007 Warsaw, Poland

Looking for antibacterial and antifungal activities of benzo[b]furan derivatives we have designed and synthesized ten hydrazide and phenylhydrazide of 2- and 3-benzo[b]furancarboxylic acids methyl esters. They were tested against Gram-negative and Gram-positive bacterial strains and *Candida albicans*. All synthesized compounds were completely inactive against tested microorganisms.

1. INTRODUCTION

It is widely known that numerous derivatives of benzofuran and dihydrobenzofuran show antiprotozoal and/or antifungal activity [1-4]. Amiodarone, a drug now in clinical use as an antiarrhythmic agent causing alterations in calcium homeostasis and cell death in yeasts is a good example of a species with antifungal activity [5-7]. Inspired by these reports, in a continuation of our research in the field of synthesis of new, biologically active benzo[b]furans [8-9] we have designed and prepared derivatives of 2- and 3-benzo[b]furancarboxylic acids methyl esters (1a-b, 2a-b, 3a-b, 4a-b and 5a-b). The methyl esters 1-5 were synthesized according to previously published paper [9]. We describe in details the synthesis of hydrazide and phenylhydrazide of 2- and 3-benzo[b]furancarboxylic acids methyl esters. The low solubility of compounds both in chloroform and DMSO resulted in NMR spectra of poor quality, therefore all of the final compounds were also characterized by ESI spectra, which were in accordance with the proposed structures.

Five newly synthesized compounds were tested for their antibacterial and antifungal activities. Gram-negative and Gram-positive bacterial strains and

Candida albicans used in this study have common application in the antimicrobial activity tests for many substances like antibiotics, disinfections and antiseptic drugs as in research on new antimicrobial agent [10-12]. All synthesized compounds were completely inactive against tested microorganisms.

2. EXPERIMENTAL

The melting point was determined in a capillary on Kofler's apparatus and is uncorrected. The ^{1}H NMR spectra were recorded in Warsaw Medical University, Pharmacy Department on a Bruker AVANCE DMX400 spectrometer, operating at 400 MHz for ^{1}H. The chemical shift values, expressed in ppm, were referenced downfield to TMS at an ambient temperature. The ESI spectra were recorded in Warsaw Institute of Organic Chemistry PAN on a Mariner PE Biosystem spectrometer or in Chemistry Department of Warsaw University on a (TOF)-LCT spectrometer. Flash chromatography was performed on Merck silica gel 60 (200–400 mesh) using chloroform/methanol (9:1 vol.) mixture as eluent. Analytical thin later chromatography was carried out on silica gel F_{254} (Merck) plates (0.25 mm thickness).

Hydrazide and phenylhydrazide derivatives of 2- and 3-benzo[b]furan-carboxylic acids methyl esters (1a-b, 2a-b, 3a-b, 4a-b, 5a-b) – general procedure

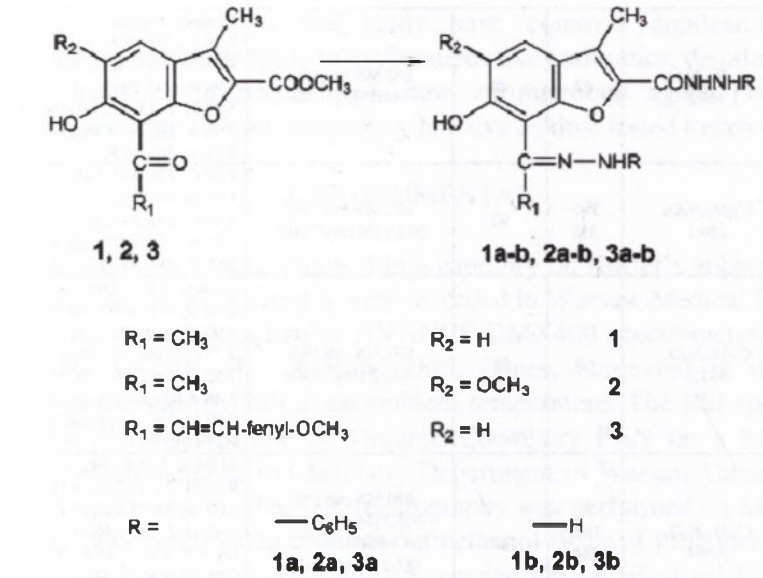
0.9 mmol appropriate methyl ester 1-5 were dissolved in 5 ml of ethanol with 0.9 mmol 80% hydrazine hydrate or phenylhydrazine (for ester 5) or 1.8 mmol 80% hydrazine hydrate or phenylhydrazide (for esters 1, 2, 3 and 4). The mixture remained in room temperature for 24 hours. Afterwards, the solution was cooled down and the compound was filtered and dried in vacuum dessicator. Physicochemical and spectral properties of compounds are presented in Table 1.

Tab. 1. Physicochemical and spectral properties of compounds.

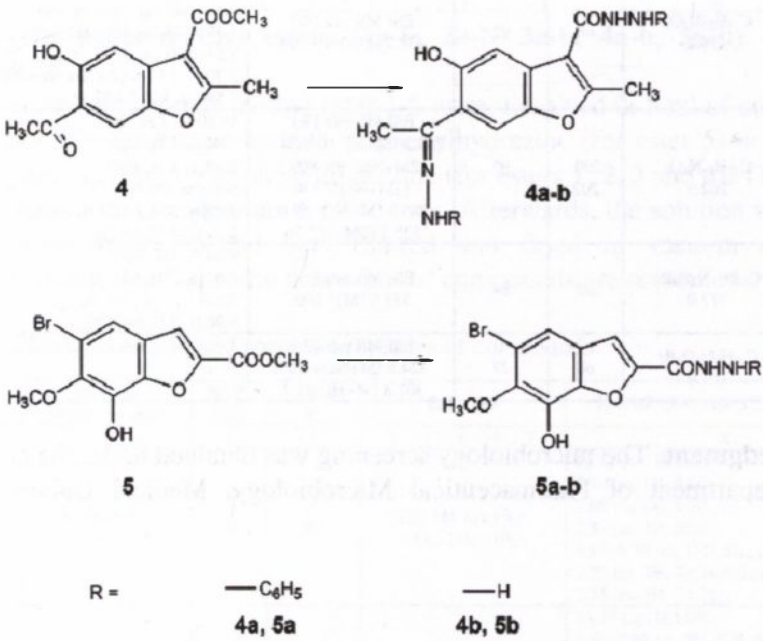
Comp. no.	Formula Molecular mass	M. P. [°C]	Yield %	ESI - MS			^{1}H NMR (400 MHz,$CDCl_3$) δ (ppm)
1	2	3	4	5	6	7	8
1a	$C_{24}H_{22}N_4O_3$ 414.2	oil	92	ESI MS m/z [%]: 414.2 $[M]^+$ 100.			13.17 (s, 1H, OH), 8.10 (m, 1H, 4-H), 7.69 (m, 1H, 5-H), 7.33 (m, 3H, NH), 6.97–6.76 (m, 10H, H_{arom}), 2.59 (m, 3H, 7-CN(NH_2)CH_3), 2.55 (m, 3H, 3-CH_3).
1b	$C_{12}H_{14}N_4O_3$ 262.1	180-182	87	ESI MS m/z [%]: 285.1 $[M+Na]^+$ 100.			13.17 (s, 1H, OH), 7.69–7,52 (m, 2H, 4-H, NH), 7.06 (m, 1H, 5-H), 6.99–6.87 (m, 4H, NH_2), 2.57 (m, 3H, 7-CN(NH_2)CH_3), 1.68 (m, 3H, 3-CH_3).

2a	$C_{25}H_{24}N_4O_4$ 444.2	oil	78	ESI MS m/z [%]: 444.2 $[M]^+$ 100.	13.64 (s, 1H, OH), 7.28 (m, 1H, 4-H), 7.17 (m, 11H, H_{arom}, NH), 6.90 (m, 4H, NH_2), 3.99 (d, J=2,0 Hz, 3H, 5-OCH_3), 2.98 (s, 3H, 7-C-CH_3), 2.58 (s, 3H, 3-CH_3),
2b	$C_{12}H_{16}N_4O_4$ 280.1	356-358	90	ESI MS m/z [%]: 303.1 $[M+Na]^+$ 100.	7.07 (s, 2 H, 4-H, NH), 6.91 (m,4H, NH_2), 3.98 (s, 3 H, 5-OCH_3), 3,02 (s, 3 H, 7-CN(NH_2)CH_3), 2.52 (s, 3 H, 3-CH_3).
3a	$C_{32}H_{28}N_4O_4$ 532.3	oil	79	ESI MS m/z [%]: 532.2 $[M]^+$ 100.	11.04 (s, 1 H, 6-OH), 8.42 (d, J=15.2 Hz, 1H, 1'H), 8.00(d, J=15.2 Hz, 1H, 2'H), 7.77 (d, 6 Hz, 1H, NH), 7.52 (d, J=6,2 Hz, 1H, NH), 7.46–6.87 (m, 16H, H_{arom}), 3.89 (s, 3 H, phenyl-OCH_3), 2.25 (s, 3 H, 3-CH_3).
3b	$C_{20}H_{20}N_4O_4$ 380.4	162-164	80	ESI MS m/z [%]: 403.2 $[M+Na]^+$ 100; 783.3 $[2M+Na]^+$ 52.1; 381.2 $[M+H]^+$ 42.8; 761.3 $[2M+H]^+$ 16.8.	11.04 (s, 1 H, 6-OH), 8.42 (d, *J* = 15.2 Hz, 1 H, 1'-H), 8.00 (d, *J* = 15.2 Hz, 1 H, NH), 7.99 (d, *J* = 15.4 Hz, 1 H, 2'-H), 7.73 (m, 3 H, 4-H, 5'-H, 6'-H), 6.99 (m, 7 H, 5-H, 3'-H, 4'-H, NH_2), 3.89 (s, 3 H, phenyl-OCH_3), 2.25 (s, 3 H, 3-CH_3).
4a	$C_{24}H_{22}N_4O_3$ 414.2	oil	92	ESI MS m/z [%]: 437.2 $[M+Na]^+$ 100.	12.18 (s, 1H, 5-OH), 7.91–7.56 (m, 3H, NH), 7.54–7.42 (m,2H, 7-H, 4-H), 7.39–6.88 (m, 10H, H_{arom}), 7.64–6.92 (m, 12 H, H_{arom}), 2.70 (s, 3 H, 6-CN(NH-arom)CH_3), 2.54 (m, 3 H, 2-CH_3).
4b	$C_{12}H_{14}N_4O_3$ 262.3	200-202	95	ESI MS m/z [%]: 263.3 $[M+H]^+$ 100; 547.2 $[2M+Na]^+$ 95; 809.3 $[3M+Na]^+$ 75.4; 285.2 $[M+Na]^+$ 59.6; 525.2 $[2M+H]^+$ 36.	10.89 (s, 1 H, NH), 7.84 (s, 1 H, 7-H), 7.49 (s, 1 H, 4-H), 6.99 (m, 4H, NH_2), 2.79 (s, 3 H, 6-CN(NH_2)CH_3), 2.29 (s, 3 H, 2-CH_3).
5a	$C_{16}H_{13}N_2O_4Br$ 377.0	oil	84	ESI MS m/z [%]: 377.0 $[M]^+$ 100.	9,94 (s, 1H, OH), 8,67 (m, 2H, NH-NH), 7.84–7.11 (m, 7H, H_{arom}), 3.96 (s, 3 H, 6-OCH_3).
5b	$C_{10}H_9N_2O_4Br$ 300.9	oil	27	ESI MS m/z [%]: 324.8 $[M+Na]$+ 100; 302.8 $[M+H]^+$ 91.7.	

Acknowledgment. The microbiology screening was obtained under the auspices of the Department of Pharmaceutical Microbiology, Medical University of Warsaw.



Scheme 1. Synthesis of the compounds 1a-b, 2a-b and 3a-b.



Scheme 2. Synthesis of the compounds 4a-b and 5a-b.

3. REFERENCES

[1] M. Mesubuchi, H. Ebiike, K. Kawasaki, S. Sogabe S, M. Satoshi, K. Morikami, *Bioorg. Med. Chem.* 114463 (2003).
[2] F. Alvarez, A. Gherardi, P. Nebois, M. E. Sarciron, A. F. Petavy, N. Walchshofer, *Bioorg. Med. Chem.* 12, 977 (2002).
[3] S. Sotheeswaran, V. Pasupathy, *Phytochemistry* 32, 1083 (1993).
[4] Y. Oshima, Y. Ueno, H. Hikino, *Tetrahedron* 46, 5121 (1990).
[5] W. E. Courchesne, S. Ozturk, *Molecular Microbiology* 47, 223 (2003).
[6] W. E. Courchesne, *The Journal of Pharmacology and Experimental Therapeutics* 300, 195 (2002).
[7] R. A. Tapia, L. Alegria, C. D.Pessoa, C. Salas, M. J. Pautet, N. Walschshoter, H. Fillion, *Bioorg. Med. Chem.* 112175 (2003).
[8] J. Kossakowski, K. Ostrowska, *Acta Polon Pharm* 63, 271 (2006).
[9] J. Kossakowski , K. Ostrowska, E. Hejchman, I. Wolska, *Il Farmaco* 60, 519 (2005).
[10] A. Orzeszko, B. Kamińska, G. Orzeszko, B. J. Starościak, *Farmaco* 55, 619 (2000).
[11] M. Furmanowa, A. M. Nosow, A. V. Oreshnikow, A. G. Kluskin, M. Kotin, B. J. Starościak, A. Śliwińska, J. Guzewska, R. Bloch, *Pharmazie* 57, 424 (2002).
[12] A. Orzeszko, B. Kamińska, B. J. Starościak, *Farmaco* 57, 619 (2002).

CURRICULA VITAE

Professor Jerzy Kossakowski was born in 1943. He studied at Warsaw University. In 1967 he obtained M.Sc. title, and started to work as scientific assistant in the Chair and Department of General Chemistry, the Medical University of Warsaw. In 1975 he presented the thesis "Synthesis of new derivatives of isovisnagine and khellin with expected pharmacological activity" and obtained the Ph.D. in pharmacy. Synthesis in the field of new derivatives of coumarins, benzofurans and benzopirans resulted in many papers and habilitation "Searching for new compounds affecting the circulation system – in the group of derivatives of furobenzopiranone, benzofuran and benzopiranone" presented in 1989. In April 1993 he was appointed to an Assistant Professor post the 1st Faculty of Medicine, the Medical University of Warsaw. Professor's scientific activity comprises investigation of the relationship between pharmacological activity and chemical structure of anxiolytic, antidepressants and β-blockers. Professor's scientific output consists of 70 papers, 7 patents and 100 communications. Professor Kossakowski is a member of the Polish Pharmaceutical Society.

Marta Struga was born in Dwikozy in 1971. She studied Chemistry (1990–1995) at Maria Curie-Skłodowska University in Lublin and was graduated in 1995 receiving M.Sc. Then she started to work as scientific assistant in the Chair and Department of Organic Chemistry, Faculty of Pharmacy of Medical University of Lublin. In 2001 she presented

the thesis "Synthesis of 1,2,4-triazole derivatives in the nucleophilic substitution reactions" and obtained the Ph.D. in pharmacy. In 2001 she started to work as a lecturer in the Chair and Department of Medical Chemistry, the Medical University of Warsaw. Fields of interest: organic synthesis, synthesis of anxiolytic, antidepressive and β-adrenolytic compounds. During the time she was a co-author of 20 publications and 27 posters.

Kinga Ostrowska was born in Warsaw in 1977. She studied Chemistry (1996–2001) at Warsaw University and graduated in 2001 receiving M.Sc. in inorganic chemistry. Then she started to work as an assistant in the Chair and Department of General Chemistry at the Medical University of Warsaw. In 2003 she started Ph.D. studies at the Medical University of Warsaw. Fields of interest: organic synthesis, synthesis of anticancer antiviral and antibacterial compounds. During the time she was a co-author of 5 publications and 14 posters.