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Synthesis of new derivatives of 5-acetyl-6-hydroxy-4-methoxybenzo[b]furan with an expected pharmacological effect

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A series of 6 new ether-linked derivatives of 5-acetyl-6-hydroxy-4-methoxybenzo[b]furan has been designed and synthesized.

1. INTRODUCTION

Cardiovascular disorders, therein coronary artery disease, represent a serious life risk and often cause death. The development of new compounds that potentially have cardiovascular activity is an interesting research area.

Compounds isolated from *Ammi Visnaga* belong to drugs used against above illnesses. They broaden coronary vessels and have a spasmolytic activity. Visnagin (4-methoxy-7-methyl-5H-furo[3,2-g][1]benzopyran-5-one) is an active component of the *Ammi Visnaga* fruit, a plant traditionally used in cardiovascular disorders [1]. Their antiarrhythmic [2], hypotensive [3] activity has been also reported.

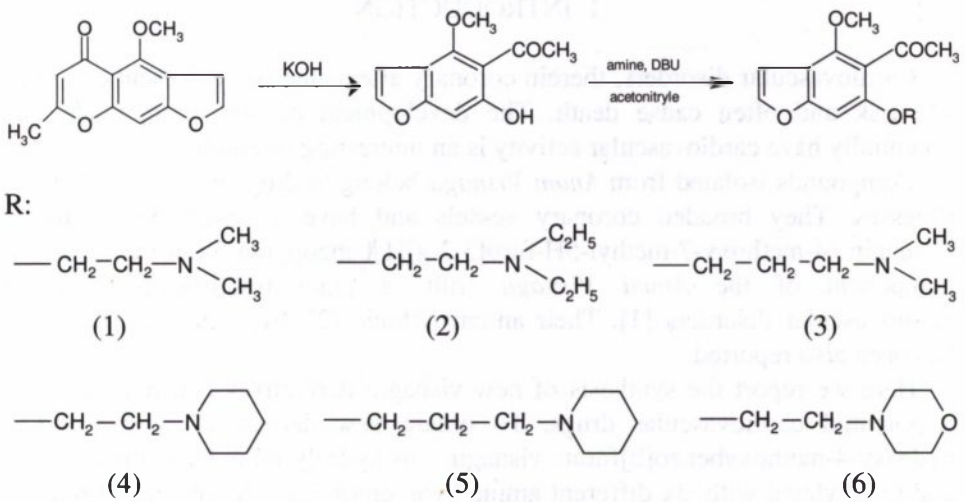
Here we report the synthesis of new visnagin derivatives that may serve as a potential cardiovascular drugs. To obtain new derivatives of 5-acetyl-6-hydroxy-4-methoxybenzo[b]furan, visnagin was hydrolysed in basic medium [1], and O-alkylated with six different amine hydrochlorides. The obtained products are presented in Scheme 1 as 1-6.

All of the final compounds were characterized by ^{1}H NMR spectra, mass spectra and elemental analysis in order to confirm expected structures.

2. EXPERIMENTAL

Melting points were determined in a capillary on Kofler's apparatus and are uncorrected. The ^{1}H NMR spectras were recorded in Medical University of Warsaw, Pharmacy Department on a Bruker AVANCE DMX400 spectrometer, operating at 400.13 MHz. Microanalyses were performed in the Microanalysis Laboratory of Warsaw Technical University and all values were within ± 0.5% of the calculated compositions. Mass spectral ESI measurements were carried out on Waters ZQ Micromass instruments with quadrupol mass analyzer. The spectra were performed in the positive ion mode at a declustering potential of 40–60V. The sample was previously separated on a UPLC column (C18) using UPLC ACQUITY™ system by Waters connected with PDA detector.

The exemplary synthesis of 5-acetyl-6-hydroxy-4-methoxybenzo[b]furane derivatives is presented in Scheme 1. Visnagin (4-methoxy-7-methyl-5H-furo[3.2g][1]benzopyran-5-one) was hydrolysed with 5% potassium hydroxide, what caused opening of the 4H-piran-4-one ring [4]. Obtained 5-acetyl-6-hydroxy-4-methoxybenzo[b]furan was subsequently O-alkylated with amine hydrochlorides to give new six compounds (1-6). Compound number 2 was also synthesized by Abdel Hafez et al. by another method [5].



Scheme 1. The general synthetic pathway.

5-acetyl-6-(O-alkyl)-4-methoxybenzo[b]furan, general procedure

The mixture of 5-acethyl-6-hydroxy-4-methoxybenzo[b]furan (1.21 mmol) and appropriate N-substituted alkylamine hydrochloride (4.84 mmol), anhydrous potassium carbonate (6.05 mmol) and DBU (0.2 mmol) were dissolved in acetonitrile (50 ml) and refluxed with stirring for 45–50 h. The reaction was monitored by TLC. When the reaction was complete, the mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel using (chloroform: methanol, 9:1) as an eluent.

5-acetyl-6-(O-ethyl-2'-dimethylamino)-4-methoxybenzo[b]furan (1)

Yield 62%; m.p. 162-164°C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.54 (d, J=2Hz, 1 H, 2-H), 6.89 (d, J=2Hz, 1 H, 3-H), 6.79 (s, 1 H, 7-H), 4.51 (d, J=4Hz, 2 H, 6-OCH_2), 4.11 (s, 3 H, 4-OCH_3), 3.38 (s, 2 H, CH_2N), 2.85 (s, 6 H, $(CH_3)_2N$), 2.50 (s, 3 H, 5-$COCH_3$),;
Anal. Calcd for $C_{15}H_{19}NO_4$: C 64.98, H 6.86, N 5.05. Found: C 64.46, H 7.07, N 5.24
ESI MS: m/z = 300.19 $[M + Na]^+$ (98%)

5-acetyl-6-(O-ethyl-2'-diethylamino)-4-methoxybenzo[b]furan (2)

Yield 58%; m.p. 145–146 °C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (s, 1 H, 2-H), 6.86 (s, 1 H, 3-H), 6.77 (s, 1 H, 7-H), 4.21 (m, 2 H, 6-OCH_2), 4.07 (m, 3 H, 4-OCH_3), 2.29 (s, 2 H, CH_2N), 2.75 (d, J=4Hz, 4 H, $(CH_2)_2N$), 2.51 (s, 3 H, 5-$COCH_3$), 1.13 (t, J=6Hz, 6 H, $(CH_3)_2N$);
Anal. Calcd for $C_{17}H_{23}NO_4$ x ¾ H_2O: C 64.05, H 7.69, N 4.39. Found: C 64.26, H 7.47, N 4.33
ESI MS: m/z = 306.20 $[M + H]^+$ (100%)

5-acetyl-6-(O-propyl-3'-dimethylamino)-4-methoxybenzo[b]furan (3)

Yield 60%; m.p. 153–154 °C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (d, J=4Hz, 1 H, 2-H), 6.88 (d, J=2Hz, 1 H, 3-H), 6.77 (s, 1 H, 7-H), 4.12 (m, 2 H, 6-OCH_2), 4.09 (s, 3 H, 4-OCH_3), 3.71 (m, 2 H, CH_2N), 2.70 (s, 6 H, $(CH_3)_2N$), 2.51 (s, 3H, 5-$COCH_3$) 2.28 (m, 2 H, CH_2-CH_2-CH_2);
Anal. Calcd for $C_{16}H_{21}NO_4$ x HCl x2H_2O: C 52.80, H 7.20, N 3.85. Found: C 52.56, H 7.31, N 3.69.
ESI MS: m/z = 292.20 $[M + H]^+$ (100%)

5-acetyl-6-(O-ethyl-2'-piperidin)-4-methoxybenzo[b]furan (4)

Yield 54%; m.p. 149–151 °C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (d, J=2Hz, 1 H, 2-H), 6.87 (s, 1 H, 3-H), 6.77 (s, 1 H, 7-H), 4.38 (s, 2 H, 6-OCH_2), 4.08 (s, 3 H, 4-OCH_3), 3.10 (s, 2 H, CH_2N), 2.85 (m, 4 H, $(CH_2)_2N$), 2.55 (s, 3 H, 5-$COCH_3$), 1.85 (m, 4H, piperidine H), 1.56 (m, 2 H, piperidine H);
Anal. Calcd for $C_{18}H_{23}NO_4$ x ½H_2O: C 66.26, H 7.36, N 4.29. Found: C 66.40, H 7.30, N 4.26.
ESI MS: m/z = 318.20 $[M + H]^+$ (100%)

5-acetyl-6-(O-propyl-3'-piperidin)-4-methoxybenzo[b]furan (5)

Yield 59%; m.p. 158–159 °C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (s, 1 H, 2-H), 6.86 (s, 1 H, 3-H), 6.77 (s, 1 H, 7-H), 4.06 (t, J=6 Hz, 2 H, 6-OCH_2), 4.03 (s, 3 H, 4-OCH_3), 2.58 (m, 6 H, $(CH_2)_3N$), 2.50 (s, 3 H, 5-$COCH_3$), 2.08 (m, 2 H, piperidine H), 1.70 (m, 4 H, piperidine H), 1.49 (m, 2 H, CH_2-CH_2-CH_2);
Anal. Calcd for $C_{19}H_{25}NO_4$ x H_2O: C 65.33, H 7.74, N 4.01. Found: C 65.06, H 7.32, N 3.97.
ESI MS: m/z = 332.50 $[M + H]^+$ (100%)

5-acetyl-6-(O-ethyl-2'-morpholine)-4-methoxybenzo[b]furan (6)

Yield 61%; m.p. 177–179 °C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (s, 1 H, 2-H), 6.87 (s, 1 H, 3-H), 6.76 (s, 1 H, 7-H), 4.26 (s, 2 H, 6-OCH_2), 4.08 (s, 3 H, 4-OCH_3), 3.82 (s, 4 H, CH_2-O-CH_2), 2.96 (s, 2 H, CH_2N), 2.74 (s, 4 H, $(CH_2)_2N$), 2.52 (s, 3 H, 5-$COCH_3$);
Anal. Calcd for $C_{17}H_{21}NO_5$ x ½H_2O: C 62.58, H 6.75, N 4,29. Found: C 62.57, H 6.78, N 4.68.
ESI MS: m/z = 320.20 $[M + H]^+$ (100%)

3. RESULTS AND DISCUSSION

Lot of benzo[b]furan derivatives have found application in treatment of coronary heart disease. Usually, small changes of a compound's molecular structure lead to significant modification of its biochemical activity. Searching for circulatory drugs, we have presently synthesized new derivatives of 5-acetyl-6-hydroxy-4-methoxybenzo[b]furan. Six new compounds were obtained. All the final compounds were characterized by ^{1}H NMR spectra, mass spectra and basis of elemental analysis which were in accordance with the proposed structures.

4. REFERENCES

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