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SYNTHESIS OF NEW DERIVATIVES OF 2,3-DIHYDRO-7-BENZO[b]FURANOL WITH POTENTIAL PHARMACOLOGICAL ACTIVITY

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Abstract: A series of 13 new ether-linked derivatives of 2,2-dimethyl-2,3-dihydro-7-benzofuranol have been designed and synthesized. Seven of them were evaluated for anti-HIV potency. They showed a relatively high cytotoxicity and a low anti-HIV-1 activity.

Keywords: 2,2-dimethyl-2,3-dihydro-7-benzofuranol, O-alkylation, antiviral activity

The design, synthesis and screening of new potential drugs for the treatment of AIDS is a significant challenge to the medical scientific community. There is a need for a continued identification and evaluation of anti-HIV potency of new agents with diverse antiviral mechanisms against HIV. Considering that, we have focused our synthetic interest on derivatives of benzo[b]furan.

A number of natural products exhibiting antiviral and antibacterial properties contain a benzofuran moiety. Substituted pterocarpan is an example of such a compound and displays antimicrobial and antitumor activities (1). Synthetic pterocarpans **1a-1f**, (Fig.1) were shown to protect cells at mM levels from the cytotoxic effects of HIV-1 (2). Unfortunately, benzofurans **2** and **3** were inactive in the evaluation of their *in vitro* anti-HIV activity (Fig.2) (3).

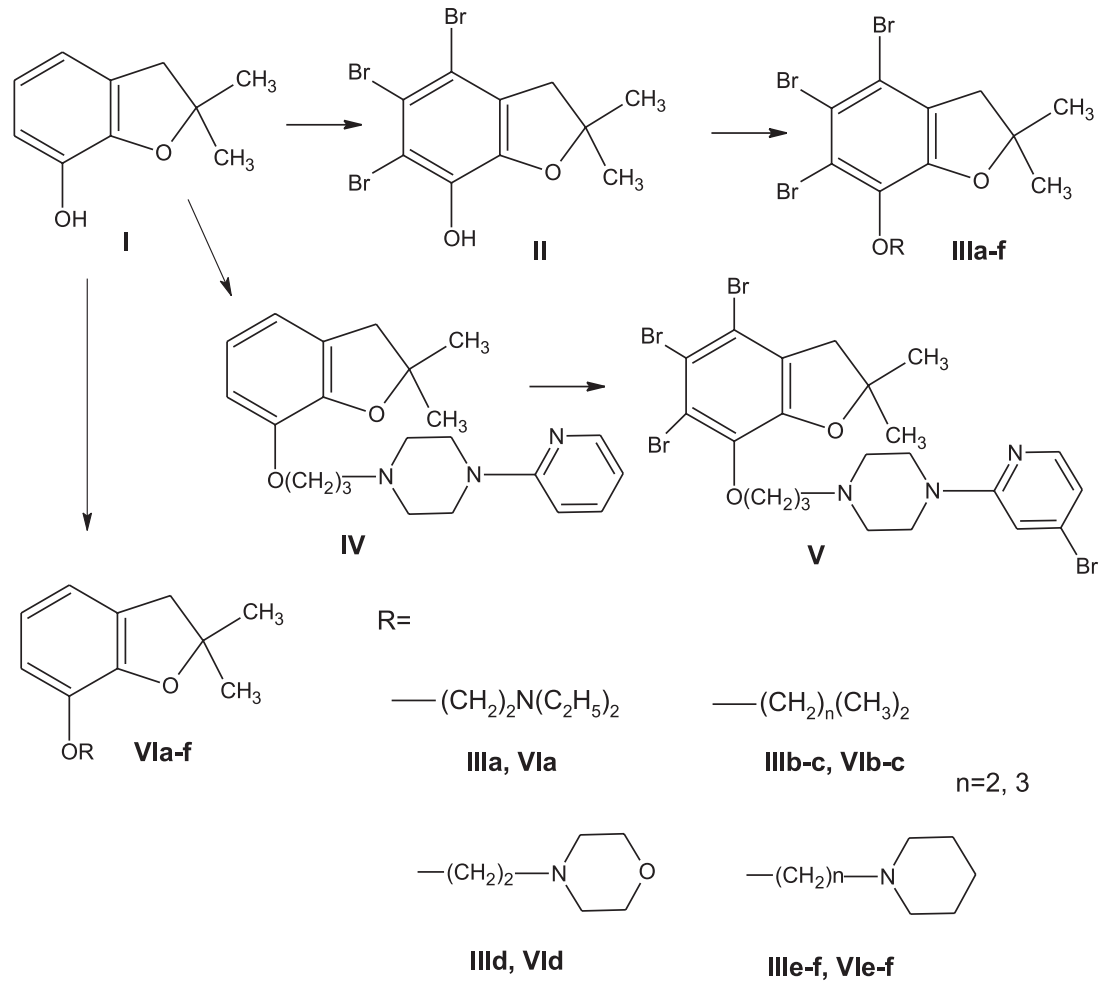
Papadaki-Valiraki et al. obtained several 7-alkoxy derivatives of 2-acetylbenzofuran (4). 1-(7-Dodecyloxy-2-benzofuranyl)ethanone (**4a,** Fig.3) and 1-(7-tridecyloxy-2-benzofuranyl) ethanone (**4b,** Fig.3) displayed a specific activity against respiratory syncytial virus in the HeLa cells and [di(2-acetyl-benzofuranyl-7-oxy]-propane (**5**, Fig.3) displayed an activity against the influenza A virus in Madin-Darby canine kidney cells. Varvaresou et al. (5) explored the antiretroviral profile of a series of new C-2 and C-7 substituted benzo[b]furans. The anti-HIV screening using acutely infected MT-4 cells showed that the dimer of 2-benzoylbenzofuran **6a** was fifteen-fold more active than its monomer congeners **7a, 7b** and **7c** and almost five-fold more potent than the monomer **7d** and the dimer **6b** (Fig.3).

Prompted by these reports we have designed and synthesized 13 new dihydrobenzofuran derivatives (6) ether-linked with an alkyl chain substituted with aliphatic or cyclic amines, for evaluation of their cytotoxicity and anti-HIV-1 activity. To increase lipophilicity of the heterocyclic component we have carried out exhaustive bromination in the benzene ring (Scheme 1). The starting material was 2,3-dihydro-2,2-dimethyl-7-benzofuranol (Aldrich) **I,** which was brominated to yield 4,5,6-tribromo-2,3-dihydro-2,2-dimethyl-7-benzofuranol **(II).** This reaction proceeded smoothly in the acetic acid at ambient temperature. The resulting phenol **II** was O-alkylated with 2-chloroalkylamines RCl under the phase transfer catalysis conditions. This reaction was carried out in acetone with Aliquat 336, in the presence of anhydrous potassium carbonate to give products **IIIa-f** (Route 1). Previously obtained compound **IV** (7) was brominated under the same conditions (Br_2/AcOH) to give the product of the substitution in the benzene ring and the 4-bromo substituted product in the pyridine system (compound **V**, Route 2). The alkylation of the phenolic moiety of compound **I** under phase transfer conditions (see Route 1) gave products **VIa-f** (Route 3). All of the final compounds were characterized by ^{1}H NMR spectra which were in accordance with the proposed structures.

The general synthetic pathway is given in Scheme 1.

EXPERIMENTAL

Melting points were determined in a capillary on Kofler's apparatus and are uncorrected. The ^{1}H NMR spectra were recorded in Warsaw Medical University, Pharmacy Department, on a Bruker AVANCE DMX400 spectrometer, operating at 400.13 MHz for ^{1}H or in the Department of Chemistry, Warsaw University, on a Varian UNITYplus-200 spectrometer, operating at 199.97



Scheme 1.

Table 1. Cytotoxicity and anti-HIV activity of selected dihydrobenzofuran derivatives.

Compound	[a]CC_{50} MT4	[b]EC_{50} HIV-1
II	60	>60
IIIb	12.4	>12.4
IIIf	6	>6
IV	47	>47

[a] Compound concentration (mM) required to reduce the viability of mock-infected MT-4 cells by 50%, as determined by the MTT method.

[b] Compound concetration (mM) required to achieve 50% protection of MT-4 cells from the HIV-1 induced cytopathogenecity, as determined by the MTT method.

MHz for ^{1}H. The chemical shift values, expressed in ppm, were referenced downfield to TMS at ambient temperature. The microanalyses were performed at the Microanalysis Laboratory of Warsaw Technical University and all the values were within ± 0.4 % of the calculated compositions.

Table 2. *In vitro* anti-HIV activity of selected dihydrobenzofuran derivatives.

Compound	IC_{50}
IIIc	2.00×10^{-4}
VIf	1.18×10^{-4}
IIIb	1.10×10^{-4}

4,5,6-Tribromo-2,3-dihydro-2,2-dimethyl-7-benzofuranol (II) and 7-[3-[4-[2-(4-bromopyridyl)]-1-piperazinyl]propoxy]-4,5,6-tribromo-2,3-dihydro-2,2-dimethylbenzofuran (**V 3HCl**)

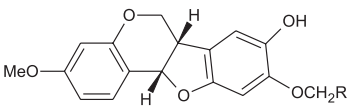
Compound I (5.26 g, 32 mmol) was dissolved in glacial acetic acid (10 mL). The solution of bromine (9.6 mL) in glacial acetic acid (20 mL) was added dropwise with stirring for 0.5 h. Stirring was contin-

Table 3. Physicochemical and spectral properties of compounds.

Comp. No.	Formula Molecular mass	M.P. [°C]	Yield %	Analyses (calc./found) %C	%H	%N	^{1}H NMR ($CDCl_3$) δ (ppm)
II	$C_{10}H_9Br_3O_2$ 400.90	146-148	93	29.90 30.01	2.25 1.80		5.44 (br.s, 1 H, 7-O<u>H</u>), 3.08 (s, 2 H, 3-<u>H</u>), 1.54 (s, 6 H, 2-CH_3)
IIIa HCl	$C_{16}H_{23}Br_3ClNO_2$ 537.10	189-190	62	35.70 35.55	4.28 4.15	2.61 2.63	4.17 (t, *J* = 6.7 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.01 (s, 2H, 3-H), 2.86 (t, *J* = 6.7 Hz, 2 H, CH_2-N), 2.62 (q, *J* = 7.1 Hz, 4 H, N(C<u>H</u>$_2$-CH_3)$_2$, 1.50 (s, 6 H, 2-CH_3), 1.04 (t, *J* = 7.1 Hz, 6 H, N(CH_2-C<u>H</u>$_3$)$_2$
IIIb HCl	$C_{14}H_{19}Br_3ClNO_2$ 508.20	201-202	62	33.05 33.26	3.74 4.03	2.75 2.50	4.16 (t, *J* = 6.0 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.01 (s, 2H, 3-H), 2.70 (t, *J* = 6.0 Hz, 2 H, C<u>H</u>$_2$-N), 2.32 (s, 6 H, (C<u>H</u>$_3$)$_2$N), 1.49 (s, 6 H, 2-CH_3)
IIIc HCl	$C_{15}H_{21}Br_3ClNO_2$ ×H_2O 540.5	202-203	61	33.30 33.73	4.25 4.03	2.59 2.41	4.13 (t, *J* = 6.3 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.00 (s, 2H, 3-H), 2.48 (t, *J* = 7.4 Hz, 2 H, C<u>H</u>$_2$-N), 2.24 (s, 6 H, (C<u>H</u>$_3$)$_2$N), 1.90 (m, 2H, CH_2-C<u>H</u>$_2$-CH_2), 1.49 (s, 6 H, 2-CH_3)
IIId HCl	$C_{16}H_{21}Br_3ClNO_3$ 550.2	205-206	63	34.89 34.89	3.82 4.36	2.54 2.47	4.29 (m, 2 H, 7-OC<u>H</u>$_2$), 3.81 (m, 4 H, C<u>H</u>$_2$-O-C<u>H</u>$_2$), 3.07-2.54 (m, 8 H, (C<u>H</u>$_2$)$_3$N, 3-H), 1.53 (s, 3 H, 2-CH_3), 1.51 (s, 3 H, 2-CH_3)
IIIe HCl	$C_{17}H_{23}Br_3ClNO_2$ ×H_2O 566.5	208-209	60	36.01 35.89	4.41 4.36	2.47 2.47	4.15 (t, *J* = 5.8 Hz, 2 H, 7-OC<u>H</u>$_2$), 2.93 (s, 2H, 3-H), 2.44 (br.s, 6 H, (C<u>H</u>$_2$)$_3$N), 1.51 (t, *J* = 4.8 Hz, 4H, piperidine-H), 1.41 (s, 6 H, 2-(CH_3)$_2$, 1.34 (d, *J* = 3.6 Hz, 2H, piperidine-H)
IIIf HCl	$C_{18}H_{25}Br_3ClNO_2$ 562.6	219	61	38.39 38.72	4.44 4.09	2.48 2.71	4.11 (t, *J* = 6.3 Hz, 2 H, 7-OC<u>H</u>$_2$), 2.98 (s, 2H, 3-H), 2.50 (t, *J* = 7.5 Hz, 2 H, CH_2-N), 2.39 (br.s, 4 H, (C<u>H</u>$_2$)$_2$N), 1.91 (m, 2H, CH_2-C<u>H</u>$_2$-CH_2), 1.57 (m, 4H, piperidine-H), 1.47 (s, 6 H, 2-CH_3), 1.40 (m, 2H, piperidine-H)
V 2HCl	$C_{22}H_{27}Br_4Cl_2N_3O_2$ 755.6	219-220	51	34.93 34.80	3.57 3.57	5.55 5.73	8.13 (d, *J* = 2.4 Hz, 1 H, Hα pyridine), 7.52 (dd, J_1 = 2.8 Hz, J_2 = 8.8 1 H, Hγ pyridine), 6.54 (d, *J* = 9.2 Hz, 1 H, Hβ pyridine), 4.18 (t, *J* = 6.4 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.52 (t, *J* = 4.8 Hz, 4 H, (CH_2)$_2$-N), 3.03 (s, 2H, 3-H), 2.63 (t, *J* = 7.2 Hz, 2 H, OCH_2-CH_2-C<u>H</u>$_2$), 2.58 (t, *J* = 4.8 Hz, 4H, (NC<u>H</u>$_2$)$_2$), 1.97 (m, 2H, OCH_2-C<u>H</u>$_2$), 1.51 (s, 6 H, 2-(CH_3)$_2$)
VIa HCl	$C_{16}H_{26}ClNO_2$ 299.5	oil	71	64.34 64.37	8.37 8.34	4.68 4.86	6.84-6.73 (m, 3 H, 4,5,6-H), 4.55 (t, *J* = 4.4 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.54-3.26 (m, 6 H, (CH_2)$_3$-N), 3.02 (s, 2H, 3-H), 1.48 (m, 6H, C<u>H</u>$_3$), 1.26 (m, 6 H, CH_3)
VIb HCl	$C_{14}H_{22}ClNO_2$ ×0.5 H_2O 280.8	oil	59	59.82 59.52	8.29 8.76	8.29 4.98	4.96 6.69 (m, 3 H, 4,5,6-H), 4.11 (t, *J* = 6.2 Hz, 2 H, 7-OC<u>H</u>$_2$), 2.93 (s, 2H, 3-H), 2.69 (t, *J* = 6.4 Hz, 2 H, CH_2-N), 2.28 (s, 6 H, N(CH_3)$_2$), 1.42 (s, 6H, C<u>H</u>$_3$)
VIc HCl	$C_{15}H_{24}ClNO_2$ ×0.25 H_2O 290.3	oil	63	61.99 62.33	8.53 8.97	44.8 82	6.72 (s, 3 H, 4,5,6-H), 4.09 (t, *J* = 6.8 Hz, 2 H, 7-OC<u>H</u>$_2$), 2.98 (s, 2H, 3-H), 2.40 (t, *J* = 7.1 Hz, 2 H, CH_2-N), 2.21 (s, 6 H, N(CH_3)$_2$), 1.96 (m, 2 H, CH_2-C<u>H</u>$_2$-CH_2), 1.48 (s, 6H, C<u>H</u>$_3$)

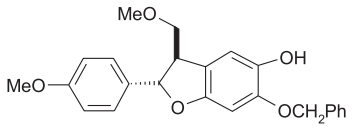
Table 3. cont.

Comp. No.	Formula Molecular mass	M.P. [°C]	Yield %	Analyses (calc./found) %C	%H	%N	^{1}H NMR ($CDCl_3$) δ (ppm)
VId HCl	$C_{16}H_{24}ClNO_3 \times 0.5\ H_2O$ 322.8	177	56	59.47 59.93	7.74 7.81	4.34 4.58	6.77 (s, 3 H, 4,5,6-H), 4.21 (t, *J* = 6.1 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.74 (t, *J* = 4.4 Hz, 4 H, C<u>H</u>$_2$-O-C<u>H</u>$_2$), 3.02 (s, 2H, 3-H), 2.81 (t, *J* = 6.4 Hz, 2 H, CH_2-N), 2.59 (m, 4 H, N(CH_2)$_2$), 1.50 (s, 6 H, 2-(CH_3)$_2$
VIe HCl	$C_{17}H_{26}ClNO_2$ 311.6	oil	55	65.46 65.09	8.34 8.89	4.49 4.23	6.70 (s, 3 H, 4,5,6-H), 4.14 (t, *J* = 6.6 Hz, 2 H, 7-OC<u>H</u>$_2$), 2.95 (s, 2H, 3-H), 2.72 (t, *J* = 6.7 Hz, 2 H, CH_2-N), 2.45 (br.s, 4 H, (C<u>H</u>$_2$)$_2$N), 1.53 (m, 4H, piperidine-H), 1.44 (s, 6 H, 2-(CH_3)$_2$, 1.39 (m, 2H, piperidine-H)
VIf HCl	$C_{18}H_{28}ClNO \times H_2O$ 345.6	oil	52	62.85 63.23	8.72 8.65	4.07 4.45	6.74 (m, 3 H, 4,5,6-H), 4.11 (t, *J* = 6.8 Hz, 2 H, 7-OC<u>H</u>$_2$), 3.01 (s, 2H, 3-H), 2.52 (t, *J* = 7.2 Hz, 2 H, CH_2-N), 2.45 (br.s, 4 H, (C<u>H</u>$_2$)$_2$N), 2.01 (m, 2 H, CH_2-C<u>H</u>$_2$-CH_2), 1.60 (m, 4H, piperidine-H), 1.50 (s, 6 H, 2-(CH_3)$_2$, 1.47 (m, 2H, piperidine-H)



1a R=α-naphthylmethyl
1b R=β-naphthylmethyl
1c R=C_6H_{11}
1d R=$CH(CH_3)_2$
1e R=Phenyl
1f R=H

Figure 1. Synthetic pterocarpans.



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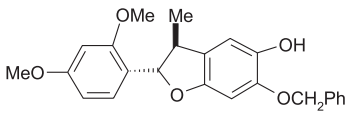

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Figure 2. 2-Aryl-2,3-dihydrobenzofuran derivatives.

ued for 8 h at ambient temperature. The reaction mixture was quenched with water (50 mL), and 10% sodium thiosulfate (50 mL) and extracted with chloroform (3x60 mL). The combined organic layers were dried over $MgSO_4$. The drying agent was removed by filtration, the solvent was evaporated and the yellow solid residue was crystallized from glacial acetic acid to give 11.95 g of compound II (93%) (Table 3).

O-Alkyl derivatives of 4,5,6-tribromo-2,3-dihydro-2,2-dimethyl-7-benzofuranol and 2,3-dihydro-2,2-dimethyl-7-benzofuranol (**IIIa-f, VIa-f**)

A mixture of a phenol (**I** or **II**, 1 mmol), an appropriate amine (3 mmol) and anhydrous potassium carbonate (6 mmol, 0.83 g) in anhydrous acetone (25 mL) was refluxed with magnetic stirring for 48 h. The reaction was monitored by TLC. Inorganic salts were removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: chloroform, chloroform-methanol). The oily residue was dissolved in methanol saturated with gaseous HCl. The hydrochloride was precipitated by addition of diethyl ether (Table 3).

RESULTS AND DISCUSSION

This work describes an efficient way to obtain new derivatives of 2,3-dihydro-2,2-dimethyl-7-ben-

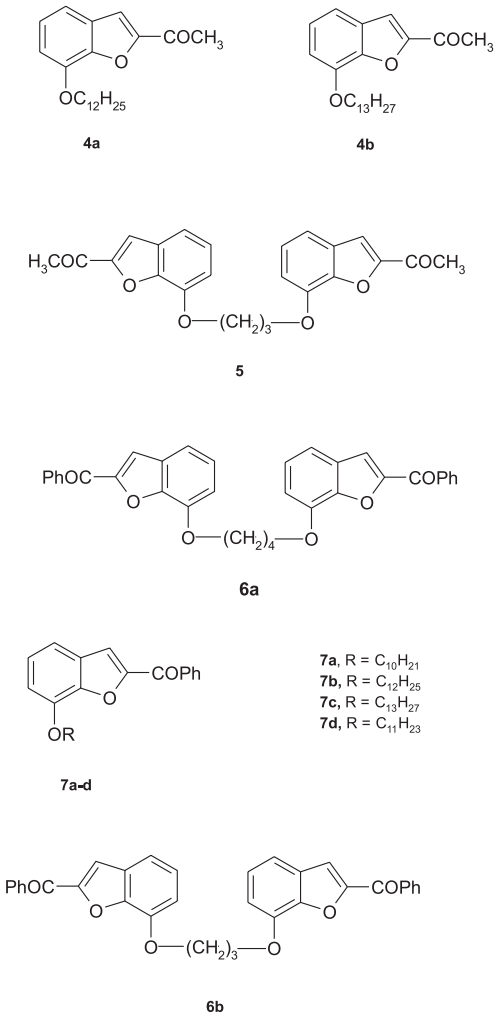

Figure 3. Series of benzofurans derivatives with anti-HIV activity.

zofuranol. Several of the synthesized compounds are evaluated for their anti-HIV-1 properties.

The compound **II, IIIb, IIIf and IV** are screened for their cytotoxicity (MT-4 cells) and anti-HIV-1 activity in Universita di Cagliari, Monserrato, Italy (8). Compound **IIIf** showed relatively low cytotoxicity. The results are shown in Table 1.

The compounds **IIIb, IIIc and VIf** were screened for their anti-HIV-1 activity in National Cancer Institute, Maryland, Bethesda (9), but none of them showed antiviral activity. The results are shown in Table 2.

Acknowledgment

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