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Structural analogs of umifenovir
2*. The synthesis and antiHIV activity study of new regioisomeric (*trans*-2-phenylcyclopropyl)-1*H*-indole derivatives

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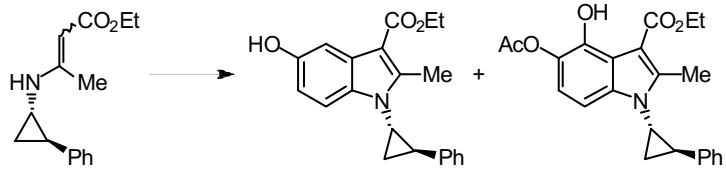
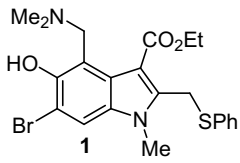


We report new carboanalogs of umifenovir – regioisomeric derivatives of ethyl 5-hydroxy-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate. The inhibition of HIV replication by umifenovir and its carboanalogs at micromolar concentration range has been demonstrated for the first time.

Keywords: umifenovir, conformationally restricted analogs, antiviral activity.

In recent years there has been an increasing number of publications about the broad spectrum of antiviral activity of umifenovir analogs,[2] obtained by modification of the original molecule according to the "Sheridan criteria".[3] Such modifications of umifenovir molecule create many opportunities for directed structural optimization.

In a continuation of our previous efforts towards the synthesis and study of new conformationally restricted structural analogs of umifenovir (**1**), the active ingredient of antiviral medicine Arbidol, we performed a study of the antiHIV-1 activity of the prototype molecule, ethyl 5-hydroxy-1-methyl-2-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate (**2**) previously described by us,[1] as well as obtained and studied two regioisomeric analogs of compound **2**: ethyl 5-hydroxy-2-methyl-1-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate (**3**) and ethyl 5-acetoxy-4-hydroxy-2-methyl-1-(*trans*-2-phenylcyclopro-



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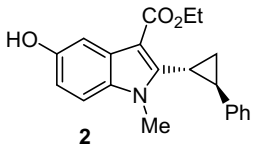

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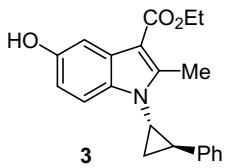

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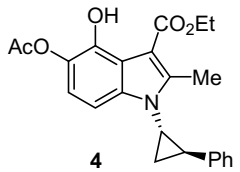

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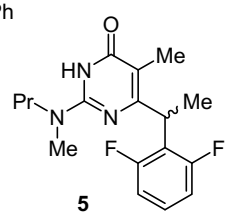

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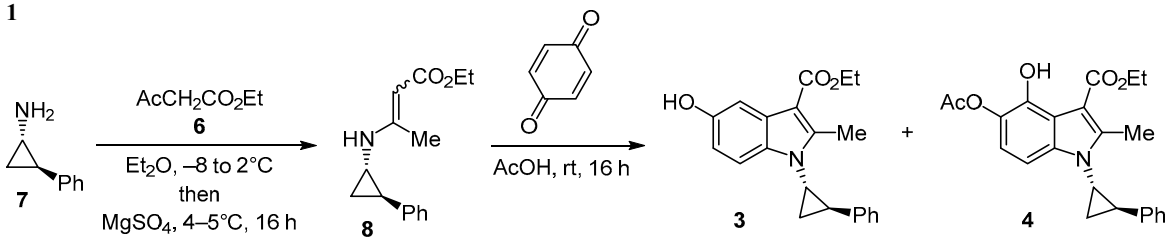
* For Communication 1, see [1].

Scheme 1



pyl)-1*H*-indole-3-carboxylate (**4**). We used our previously obtained non-nucleoside type HIV replication inhibitor *rac*-MC-1501 (**5**)[4,5] as an external reference standard.

The synthesis of regioisomeric analog of compound **2**, in which the locations of the methyl group and *trans*-2-phenylcyclopropyl group were switched, was achieved from ethyl 3-oxobutanoate (**6**) and *trans*-2-phenylcyclopropylamine (**7**) (Scheme 1). The latter was obtained according to the method of Grinshtein and Anderson.[6] At the first stage, these two reagents were converted to the enaminoester **8**. The condensation occurred in anhydrous Et_2O, using $MgSO_4$ as dehydrating agent. We should note that the attempt to perform this reaction analogously to the interaction of compound **6** with $BzNH_2$ in refluxing toluene in the presence of a catalytic amount of TsOH[7] did not give the desired result. Instead of the target product, its mixture with two thermal cyclocondensation products was obtained. These compounds probably were pyridine derivatives, as indirectly confirmed by the results of HPLC-MS analysis.

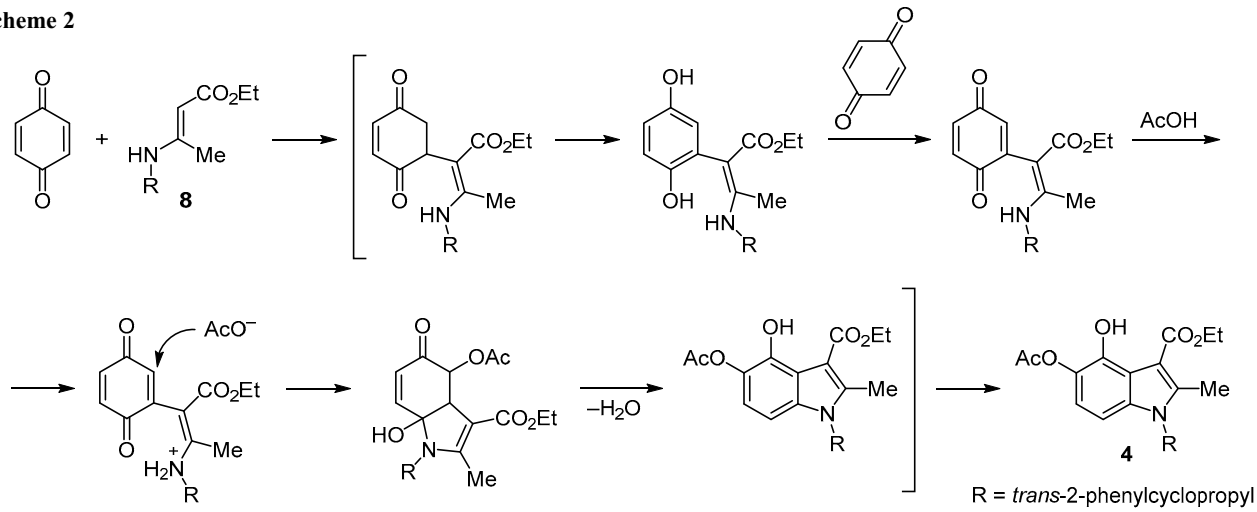
The enaminoester **8** tended to undergo secondary transformations, thus it was not isolated in pure form, but was further used as a solution in Et_2O.

According to data published by American authors,[8] the yield of indole derivatives in a Nenitzescu reaction was substantially increased by using a twofold molar excess of 1,4-benzoquinone. We verified this approach by treating the obtained enaminoester **8** with 1,4-benzoquinone (as a solution in AcOH). The crude reaction product was separated by preparative chromatography, resulting in the isolation of two indole derivatives, one of which was the target compound **3**, while the other was its 5-acetoxy-4-hydroxy-substituted analog **4**.

The obtained compounds were structurally characterized by HPLC-MS, two-dimensional NMR techniques, and IR spectroscopy. In the case of ethyl 5-hydroxy-2-methyl-1-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate (**3**), the molecular structure was established from NMR dataset, including 2D and 1D experiments. The one-dimensional ^1H NMR spectrum featured signals due to hydroxy, ethoxy, and methyl groups, the cyclopropane ring, as well as the protons of phenyl group and the substituted indole ring. There were 19 different carbon atom singals in ^{13}C NMR spectrum, including that of one carboxyl group. The two-dimensional NOESY and ^1H–^{13}C HMBC spectra enabled complete assignment of all ^1H and ^{13}C NMR signals. NOESY spectrum allowed to establish the substitution pattern in the cyclopropane ring. The coupling of 3-CH_{exo} proton in the cyclopropane ring with H-7 proton in the indole ring, 2-CH proton in the cyclopropane ring, and 2-CH_3 protons in the indole ring, as well as the coupling of 3-CH_{endo} proton in the cyclopropane ring with 1-CH proton in the cyclopropane ring and H-2,6 protons in the phenyl ring in the absence of other correlations indicated a *trans*-substitution pattern in the cyclopropane ring. The *trans* configuration of the vicinally disubstituted cyclopropane moiety in compound **4** was confirmed by analogous approach. The complete structural characterization of compound **4** was possible only by using NMR spectra acquired in $CDCl_3$ and C_6D_6. The spectra in deuterated benzene were necessary for clear interpretation of H-6,7 protons of indole ring, which was otherwise difficult due to signal overlap in deuterated chloroform.

The obtained spectra of compound **4** allowed to conclude that the indole ring positions 6 and 7 were definitely unsubstituted, since the spectra contained signals of the respective hydrogen atoms with a spin-spin coupling constant of 8.7 Hz, which is possible only for spin-spin coupling through three, but not four covalent bonds. Besides that, one of these hydrogen atoms in NOESY spectrum gave a prominent cross peak with 1-CH and 3-CH_{exo} protons of the cyclopropane ring, confirming that this hydrogen atom was located at the indole ring position 7. An argument against the presence of acetoxy group at the indole ring position 4 was found in the hydroxyl proton cross peak with carbon atoms. Taking into account that ^1H–^{13}C HMBC spectra reflect coupling through two, three, and in some cases four bonds, the presence of a hydroxyl group at the indole ring position 5 (expected from the usual course of Nenitzescu reaction) should be manifested as cross peaks with the C-4, C-5, and C-6 carbon atoms in the indole moiety. At the same time, ^1H–^{13}C HMBC spectra in each of the solvents showed that the hydroxyl group proton was not correlated with any of the carbon atoms forming a CH bond. On the contrary, correlations were observed only with the quaternary carbon atoms, indicating the absence of other protons next to the hydroxyl group. NOESY spectrum also lacked the coupling expected for a 5-hydroxy derivative between the hydroxyl proton and the indole ring H-6 hydrogen atom, but contained a cross signal between the hydroxyl group proton and methylene group protons of the COOEt substituent at indole ring position 3, along with a cross signal of acetoxy protons with the indole ring H-6 proton. Thus, the obtained dataset along with the absence of other cross signals that would contradict the proposed structure allowed us to establish the position of acetoxy group at position 5 of indole heterocycle. This conclusion was additionally supported by a weak correlation between the acetyl group protons and the indole ring C-5 atom in ^1H–^{13}C HMBC spectrum, while the C-5 atom gave strong

Scheme 2



cross peaks with the H-6 and H-7 protons. In the alternative structure where the acetoxy group would be linked to the C-4 atom of indole heterocycle, the H-7 proton would not produce such a cross signal due to separation by 4 bonds.

Thus, the observed correlations allowed to determine that the reaction gave not only the target product **3**, but also the 5-acetoxy-4-hydroxy isomer **4**. Thus, the performed reactions followed Scheme 1.

The formation of by-product **4** was likely associated with an oxidative acetoxylation reaction involving the solvent and an excess of 1,4-benzoquinone, and this process was concluded with intramolecular trans-esterification. The potential reaction mechanism can be represented by Scheme 2.

Remarkably, such a course of this reaction does not exactly follow the literature precedents. On one hand, Bell and coauthors[8] synthesized ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate in a Nenitzescu reaction between 2 equiv of 1,4-benzoquinone and 1 equiv of ethyl 3-amino-crotonate in AcOH, obtaining the desired product in 62% yield. The 5-acetoxy-4-hydroxy derivative was not obtained. On the other hand, according to publications by Kucklander,[9,10] the Nenitzescu reaction gave specifically 5-acetoxy-4-hydroxy derivatives of indole, but with only indirectly characterized structures (based on mass spectra, IR and ^{1}H NMR spectra, and elemental analysis). Furthermore, in the case of a reaction between equimolar amounts of 1,4-benzoquinone and ethyl 3-anilinocrotonate (unsubstituted in the aromatic ring, or containing a chlorine, methoxy or nitro group at the *para*-position) in AcOH, the respective ethyl 5-acetoxy-4-hydroxy-1-phenyl-1*H*-indole-3-carboxylates were isolated in approximately 5% yields.[9] At the same time, the reaction of ethyl 3-(methylamino)crotonate with a twofold molar excess of 1,4-benzoquinone in AcOH gave a 15% yield of ethyl 5-acetoxy-4-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylate[10] (the reaction of equimolar amounts of the same reagents in acetone led to the formation of ethyl 5-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylate in 48% yield,[11] or 46% yield when performing the reaction in 1,2-dichloroethane[12]). There were no X-ray structural data or two-dimensional NMR spectra in the publications by Kucklander. For this reason, Allen proposed the more likely formation of 4-acetoxy-5-hydroxy derivatives and the absence of a transesterification stage.[13] Finally, during the preparation of compound **2** in AcOH, HPLC-MS and HPLC-MS/MS analyses of the reaction product mixture did not reveal the presence of a compound giving a molecular ion that would match a 5-acetoxy-4-hydroxy-substituted compound.[1]

Thus, taking into account the unpredictability of Nenitzescu reaction results in glacial acetic acid, we have to agree with the results reported by Pawlak and coauthors,[14] in that the optimum solvent for this process is $MeNO_2$, a polar solvent with high dielectric permittivity and less tendency for side reactions, unlike AcOH.

Our obtained indole derivatives, along with the reference compounds, umifenovir (**1**) (as monohydrate of hydrochloride) and *rac*-MC-1501 (**5**), were tested for anti-HIV activity (Table 1).

The obtained data indicate that the synthesized umifenovir analog **2** exhibits antiHIV-1 and antiHIV-2 activity in single digit micromolar concentration range. The antiHIV-1 activity of this compound is noticeably lower than that of compound **5**, but its antiHIV-2 activity is higher. Besides that, the ability of umifenovir (**1**) to suppress the replication of HIV-1 in single digit micromolar concentration range was demonstrated for the first time. At the same time, this compound showed pronounced cytotoxic properties in combination with a lack of antiHIV-2 activity over the studied concentration range.

Remarkably, the switching of methyl and cyclopropyl group positions in the molecule of compound **2** gave a compound that also lacked noticeable cytotoxicity, but was capable of suppressing the replication of HIV-1 in micromolar concentration range. At the same time, such a change led to the loss of antiHIV-2 activity for this compound. However, 5-acetoxy-4-hydroxy derivative **4** maintained the ability to suppress replication of both HIV-1 and HIV-2, but at the same time exhibited significantly higher cytotoxicity than compound **3**.

The antiHIV-1 activity of the obtained compounds could be explained by the structural similarity of their molecules to

Table 1. The study of antiHIV-1 and antiHIV-2 activity of compounds **1**–**5** in infected MT-4 lymphoid tissue cell culture

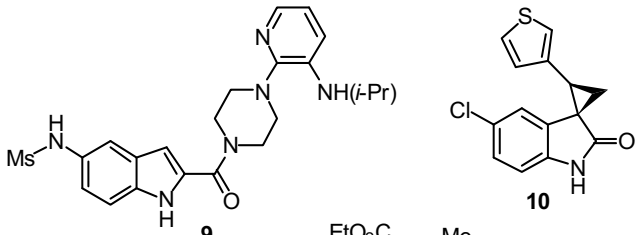
Compound	HIV-1 (strain NL-4.3) EC_{50}*, μM	HIV-2 (strain ROD) EC_{50}*, μM	MT-4 CC_{50}**, μM	SI*** (HIV-1)	SI*** (HIV-2)
1·HCl·H₂O	20.32	>8.4	23	1.1	<2.7
2	3.58	5.4	>298	>83.3	>55.2
3	5.91	>250	>250	>42.3	–
4	6.37	11.09	50	~7.8	~4.5
5	0.0019	8.6	>311	>163737	>36

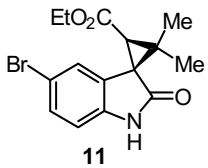
* The effective concentration of compound that ensured the required result in 50% of the used live cells.
** The cytotoxic concentration of compound, at which only 50% of cells survive.
*** The ratio of CC_{50} to EC_{50}.

that of delavirdine (**9**), [15] a non-nucleoside inhibitor of HIV-1 reverse transcriptase, approved for clinical use. Besides that, some derivatives of 2-heteroaryl- (**10**) and 2-(carbethoxy)-5'-halospiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one (**11**) also possess antiHIV-1 activity.[16,17]

Thus, for our synthesized compounds, as well as for umifenovir (**1**), delavirdine (**9**), and experimental derivatives of 5'-halo-2-heteroarylspiro[cyclopropane-1,3'-indol]-2'(1'*H*)-one **10**, **11**, there is a tendency for bioisosteric relative arrangement of indole and benzene (or heteroaromatic) rings. This structural motif probably plays the role of pharmacophore in this case. At the same time, the introduction of a substituent at indole ring position 4 (in the cases of umifenovir (**1**) and compound **4**) enhanced the cytotoxicity of the obtained compounds.

With regard to the antiHIV-2 activity of our obtained compounds, it could not be likely explained by the similarity to compounds **9**–**11**. For this reason, further studies are needed for establishing the exact molecular mechanism for biological activity of our obtained indole derivatives against HIV-1, as well as against HIV-2.





Thus, we have proved for the first time that the use of a twofold molar excess of 1,4-benzoquinone in the Nenitzescu indole synthesis may lead to the formation of 5-acetoxy-4-hydroxy-substituted by-products, probably linked to the oxidative potential of 1,4-benzoquinone. Besides that, the antiHIV-1 activity of umifenovir hydrochloride monohydrate in micromolar concentration range was identified for the first time. Thus, a new lead compound has been discovered for the structure-activity relationship study and directed design of non-nucleoside antiviral agents, ethyl 1-methyl-1*H*-indole-3-carboxylate, containing the *trans*-2-phenylcyclopropyl moiety in the heteroaromatic system.

Experimental

IR spectra of the obtained compounds were recorded on a Specord M-82 spectrometer in Nujol. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II 600 spectrometer (600 and 150 MHz, respectively), equipped with an inverse probe with *Z*-axis gradient coil. The solvents were DMSO-d_6 (at 25°C, compound **3**), $CDCl_3$ and C_6D_6 (at 30°C, compound **4**); the residual solvent protons and solvent carbon atoms were used as internal standards for ^{1}H and ^{13}C nuclei, respectively: 2.50 and 39.5 ppm (for DMSO-d_6), 7.27 and 77.0 ppm (for $CDCl_3$), 7.16 and 128.0 ppm (for C_6D_6). Two-dimensional experiments were performed according to Bruker standard methods by using *Z*-gradient pulse sequences. The mixing time in NOESY spectrum was 0.7 s. ^{1}H–^{13}C HMBC experiments were optimized for ^{1}H–^{13}C spin-spin coupling constants of 8.0 Hz. Routine HPLC control was performed on a chromatography system consisting of Jasco PU-980 solvent pumps, a Jasco UV-975 UV/Vis detector, and a Rheodyne injection valve under the following conditions: Reprosil C18 AQ column, 150 × 4.6 mm, 3 μm, H_2O–MeCN–85% H_3PO_4 mobile phase (200:200:1), flow rate 0.75 ml/min, detection wavelength 220 nm, t = 30°C. HPLC-MS analyses were performed on an Agilent 1200 instrument under the following conditions: Reprosil-Pur Basic C18 column, 250 × 4.6 mm, 5 μm (Dr. Maisch GmbH); eluents: A) 0.01% CF_3COOH–H_2O, B) 0.01% CF_3COOH–MeCN, gradient: 5% B (0 min), 100% B (20 min), 100% B (22 min), 5% B (22.5 min), 5% B (30 min). The column was equilibrated prior to analysis with a mobile phase containing 5% B. The flow rate was 1 ml/min, detection with a VWD single wavelength UV-Vis detector, SEDEX 85 ELSD detector (ELSD – 60°C, 3.1 bar), Agilent 6310 Ion Trap LCMS (in positive ion and MS/MS modes). Electrospray ionization was used in the mass spectrometric analysis. Elemental analysis was performed on a vario EL cube instrument. Melting points were determined by capillary method on a Buchi M-565 apparatus, the heating rate was 1°C/min (corrected melting points are reported). Merck DC-Alufolien Kieselgel 60 F_{254} plates were used for TLC,

visualization under UV light (254 nm). Column chromatography was performed on L14002 silica gel (Alfa Aesar) (0.06–0.20 mm, 70–230 mesh).

Umifenovir hydrochloride monohydrate (**1**) was obtained according to a published procedure.[1] Reagents and solvents from Alfa Aesar and Acros Organics were used for all syntheses. The solvents were dried according to standard procedures.[18] Antiviral activity studies were conducted according to the literature method.[19] Cell colonies were supplied by the Catholic University of Leuven, Belgium.

Ethyl 5-hydroxy-1-methyl-2-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate (2) was obtained according to a published procedure.[1] IR spectrum, ν, cm^{-1}: 1222, 1252, 1276, 1414, 1504, 1654, 1684, 3292.

Ethyl (2*EZ*)-3-[(*trans*-2-phenylcyclopropyl)amino]-buten-2-oate (8). A solution of ester **6** (4.5 ml, 4.6 g, 35.6 mmol) in Et_2O (75 ml) was cooled to –8°C, stirred, and treated by dropwise addition of amine **7** (4.6 g, 34.5 mmol) dissolved in Et_2O (25 ml). The obtained mixture was stirred without removing the cooling bath. When the reaction mixture temperature reached 2°C, anhydrous $MgSO_4$ was added (5 g, 41.7 mmol). The mixture was stirred and left overnight in a refrigerator at 4–5°C. The drying agent was removed by filtration, the obtained solution was further used without additional purification.

Ethyl 5-hydroxy-2-methyl-1-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate (3) and ethyl 7-acetoxy-5-hydroxy-2-methyl-1-(*trans*-2-phenylcyclopropyl)-1*H*-indole-3-carboxylate (4). A solution of 1,4-benzoquinone (7.5 g, 69.4 mmol) in AcOH (125 ml) was stirred at room temperature and treated by dropwise addition of the obtained enaminoester **8** solution in Et_2O. The reaction mixture temperature reached 36°C. The obtained mixture was left overnight at room temperature. A solution of K_2CO_3 (140 g) in H_2O (280 ml) was added dropwise to the stirred mixture. The obtained mixture was filtered, the precipitated product was washed on filter with H_2O, ground, and air-dried until constant mass. The dried product was dissolved in a minimum amount of EtOAc, adsorbed on silica gel (75 g) and separated by silica gel flash chromatography with EtOAc–hexane gradient (from 5 to 30% by volume). The fractions containing compounds **4** and **3** (R_f 0.62 and 0.56, respectively, eluent 1:4 EtOAc–hexane), were collected separately and evaporated to dryness. Compound **3** was recrystallized from MeCN, compound **4** – from toluene.

Compound 3. Yield 1.3 g (23%), pinkish crystals, mp 182–184°C. HPLC: assay 100% (t_R 19.744 min). IR spectrum, ν, cm^{-1}: 1222, 1252, 1330, 1414, 1438, 1468, 1486, 1504, 1696, 3280. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.67–1.70 (1H, m, 3'-CH_{exo}); 1.76 (1H, q, *J* = 6.6, 3'-CH_{endo}); 2.49–2.52 (1H, m, 2'-CH); 2.72 (3H, s, 2-CH_3); 3.46–3.48 (1H, m, 1'-CH); 4.27 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 6.69 (1H, dd, *J* = 2.4, *J* = 8.7, H-6); 7.26 (1H, t, *J* = 7.5, H-4 Ph); 7.27 (1H, d, *J* = 8.7, H-7); 7.31 (2H, d, *J* = 7.6, H-2,6 Ph); 7.37 (2H, t, *J* = 7.6, H-3,5 Ph); 7.40 (1H, d, *J* = 2.4, H-4); 8.93 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 12.9 (2-CH_3); 14.4 ($OCH_2\underline{C}H_3$); 17.2 (3'-CH_2); 24.4 (2'-CH); 34.7 (1'-CH); 58.6 ($O\underline{C}H_2CH_3$); 102.7 (C-3); 105.6 (C-4); 110.9 (C-6); 111.4 (C-7); 125.8 (C-2,6 Ph); 126.2 (C-4 Ph); 127.5 (C-3a); 128.5 (C-3,5 Ph); 130.7 (C-7a); 139.9 (C-1 Ph); 146.9 (C-2); 152.6 (C-5); 164.9 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 336.3 $[M+H]^+$ (100). Found, %: C 74.99; H 6.29; N 3.88. $C_{21}H_{21}NO_3$. Calculated, %: C 75.20; H 6.31; N 4.18.

Compound 4. Yield 1.4 g (10%), white crystals, mp 176–177°C. HPLC: assay 100% (t_R 22.051 min). IR spectrum, ν, cm^{-1}: 1132, 1240, 1366, 1414, 1456, 1684, 1798. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.42 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.69–1.73 (1H, m, 3'-CH_{exo}); 1.75 (1H, q, *J* = 5.2, 3'-CH_{endo}); 2.37 (3H, s, $COCH_3$); 2.44–2.47 (1H, m, 2'-CH); 2.76 (3H, s, 2-CH_3); 3.32–3.35 (1H, m, 1'-CH); 4.41 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 6.92 (1H, d, *J* = 8.7) and 6.94 (1H, d, *J* = 8.7, H-6,7);* 7.23 (2H, d, *J* = 7.3, H-2,6 Ph); 7.31 (1H, t, *J* = 7.4, H-4 Ph); 7.40 (2H, t, *J* = 8.2, H-3,5 Ph); 11.67 (1H, s, OH). ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.00 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.04–1.06 (1H, m, 3'-CH_{exo}); 1.06–1.08 (1H, m, 3'-CH_{endo}); 1.83–1.86 (1H, m, 2'-CH); 2.05 (3H, s, $COCH_3$); 2.29 (3H, s, 2-CH_3); 2.57–2.60 (1H, m, 1'-CH); 4.01 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 6.73 (1H, d, *J* = 8.7, H-7); 6.86 (2H, d, *J* = 7.2, H-2,6 Ph); 7.05 (1H, d, *J* = 8.7, H-6); 7.08 (1H, t, *J* = 7.4, H-4 Ph); 7.15–7.19 (2H, m, H-3,5 Ph); 12.28 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2 (2-CH_3); 14.4 ($OCH_2\underline{C}H_3$); 18.1 (3'-CH_2); 20.8 ($CO\underline{C}H_3$); 25.6 (2'-CH); 35.1 (1'-CH); 61.4 ($O\underline{C}H_2CH_3$); 101.3 (C-7); 104.8 (C-3); 116.3 (C-3a); 118.5 (C-6); 125.9 (C-2,6 Ph); 126.9 (C-4 Ph); 128.9 (C-3,5 Ph); 136.6 (C-7a); 139.0 (C-1 Ph); 143.4 (C-4); 146.3 (C-2); 132.4 (C-5); 168.9 (COOEt); 169.9 ($\underline{C}OCH_3$). ^{13}C NMR spectrum (C_6D_6), δ, ppm: 13.6 (2-CH_3); 13.9 ($OCH_2\underline{C}H_3$); 17.8 (3'-CH_2); 20.3 ($COCH_3$); 25.0 (2'-CH); 34.4 (1'-CH); 60.9 ($O\underline{C}H_2CH_3$); 101.0 (C-7); 104.5 (C-3); 116.6 (C-3a); 118.8 (C-6); 125.8 (C-2,6 Ph); 126.5 (C-4 Ph); 128.7 (C-3,5 Ph); 136.4 (C-7a); 139.4 (C-1 Ph); 143.4 (C-4); 145.9 (C-2); 133.5 (C-5); 168.7 (COOEt); 168.9 ($\underline{C}OCH_3$). Mass spectrum, *m/z* (I_{rel}, %): 394.9 $[M+H]^+$ (100). Found, %: C 69.97; H 6.00; N 3.70. $C_{23}H_{23}NO_5$. Calculated, %: C 70.22; H 5.89; N 3.56.

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References

1. Balzarini, J.; Ruchko, E. A.; Zakharova, E. K.; Kameneva, I. Yu.; Nawrozkij, M. B. *Chem. Heterocycl. Compd.* **2014**, *50*, 489. [*Khim. Geterotsikl. Soedin.* **2014**, *50*, 537.]

* The unambiguous assignment is not possible due to the proximity of the signals for protons H-6 and H-7 of the indole moiety.

2. Blaising, J.; Polyak, S. J.; Pécheur, E.-I. *Antivir. Res*. **2014**, *107*, 84.
3. Sheridan, R. P. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 103.
4. Mai, A.; Artico, M.; Rotili, D.; Tarantino, D.; Clotet-Codina, I.; Armand-Ugón, M.; Ragno, R.; Simeoni, S.; Sbardella, G.; Nawrozkij, M. B.; Samuele, A.; Maga, G.; Esté, J. A. *J. Med. Chem.* **2007**, *50*, 5412.
5. Rotili, D.; Samuele, A.; Tarantino, D.; Ragno, R.; Musmuca, I.; Ballante, F.; Botta, G.; Morera, L.; Pierini, M.; Cirilli, R.; Nawrozkij, M. B.; Gonzalez, E.; Clotet, B.; Artico, M.; Esté, J. A.; Maga, G.; Mai, A. *J. Med. Chem.* **2012**, *55*, 3558.
6. Grinshtein, V. Ya.; Anderson, M. Ya. *Izv. Akad. Nauk Latv. SSR*, *Ser. Khim.* **1963**, *1*, 106.
7. *Organicum* [Russian translation]; Reutov, O. A., Ed.; Mir: Moscow, 1992, Vol. 2, p. 69.
8. Bell, M. R.; Oesterlin, R.; Beyler, A. L.; Harding, H. R.; Potts, G. O. *J. Med. Chem.* **1967**, *10*, 264.
9. Kucklander, U. *Arch. Pharm.* **1971**, *304*, 602.
10. Kucklander, U. *Tetrahedron* **1972**, *28*, 5251.
11. Grinev, A. N.; Kul'bovskaya, N. K.; Terent'ev, A. P. *Zh. Obshch. Khim.* **1955**, *25*, 1355.
12. Grinev, A. N.; Yermakova, V. N.; Terent'ev, A. P. *Zh. Obshch. Khim.* **1962**, *32*, 1948.
13. Allen, G. R., Jr. *Org. React.* **1973**, *20*, 385.
14. Pawlak, J. M.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1996**, *61*, 9055.
15. Romero, D. L.; Morge, R. A.; Genin, M. J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I. W.; Reusser, F.; Thomas, R. C.; Tarpley, W. G. *J. Med. Chem.* **1993**, *36*, 1505.
16. Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105.
17. Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109.
18. Tietze, L. F.; Eicher, T. *Preparative Organic Chemistry. Reactions and Syntheses in the Organic Chemistry Laboratory* [Russian translation]*;* Alekseeva, Yu. E., Ed.; Mir: Moscow, 1999.
19. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309.