Synthesis and structure of fluoroindole nucleosides[1]

Jelena Božilović, Jan W. Bats, and Joachim W. Engels

Abstract: Chemically modified bases are frequently used to stabilize nucleic acids, to study the driving forces for nucleic acid structure formation, and to tune DNA and RNA hybridization conditions. Nucleoside analogues are chemical means to investigate hydrogen bonds, base stacking, and solvation as the three predominant forces that are responsible for the stability of nucleic acids. To obtain deeper insight into the contributions of these interactions to RNA stability, we decided to synthesize some novel nucleic acid analogues where the nucleobases are replaced by fluoroindoles. Fluorinated indoles can be compared with fluorinated benzimidazoles to determine the role of nitrogen in five-membered ring systems. The synthesis of fluoroindole ribonucleosides as well as the X-ray crystal structures of all synthesized fluoroindole ribonucleosides are reported here. These compounds could also be building blocks for a variety of biologically active RNA analogues.

Key words: indoles, nucleosides, crystal structure, glycosilation, indole-synthesis.

Résumé : Des bases chimiquement modifiées sont souvent utilisées pour stabiliser les acides nucléiques, pour étudier la force motrice pour la formation de la structure d'acides nucléiques et pour ajuster les conditions d'hybridation de l'ADN et de l'ARN. Les analogues de nucléosides sont des méthodes chimiques d'étudier les liaisons hydrogènes, l'empilement des bases et la solvatation comme les trois forces prédominantes, responsables de la stabilité des acides nucléiques. Afin de mieux évaluer les contributions de ces interactions à la stabilité de l'ARN, on a effectuer la synthèse de nouveaux analogues de l'acide nucléique dans lesquels les nucléobases sont remplacées par de fluoroindoles. On peut comparer les fluoroindoles aux benzimidazoles fluorés pour déterminer le rôle de l'azote dans le système cyclique à cinq chaînons. On rapporte la synthèse des ribonucléosides de fluoroindoles ainsi que les structures déterminées par diffraction des rayons X de tous les ribonucléosides de fluoroindoles. Ces composés pourraient aussi être utilisés dans la synthèse d'une variété d'analogues de l'ARN biologiquement actifs.

Mots-clés : indoles, nucléosides, structure cristalline, glycosilation, synthèse de l'indole.

[Traduit par la Rédaction]

Introduction

A series of fluorobenzimidazole nucleosides has been synthesized earlier and we reported the stabilizing contribution of a C–F···H–C bond (1, 2). The inability of fluorine to compete with stronger hydrogen bond acceptors, such as oxygen and nitrogen, is due to its low polarizability and contracted lone pairs. The fluorobenzimidazole analogues investigated so far all show very similar properties. Indole structure is present in a variety of natural compounds, such as amino acids, alkaloids, etc. The position of fluorine as shown by the dipole moments (Fig. 1) has a greater influence on charge distribution for fluoroindoles than for fluorobenzimidazoles. Thus, we decided to synthesize and evaluate a similar pattern of substitution on fluoroindoles (Fig. 1). To the best of our knowledge, the ribofluoro–indole compounds have not been synthesized and evaluated, though some deoxy compounds have recently been under investigation. The thermodynamic and spectroscopic studies give no information on the fine structure and conformational dynamics of fluorobenzimidazole-containing RNA. Such information would be a valuable comparison to determine the influence of nitrogen in the five-membered ring. As the charge distribution and dipole moments between those two classes of compounds differ significantly, we also expected to observe differences in RNA oligonucleotide stability as a result of containing those building blocks. Here we report strategies for the synthesis (3) of fluoroindole building blocks and the X-ray crystal structures of all synthesized fluoroindole ribonucleosides.

Received 9 January 2007. Accepted 18 February 2007. Published on the NRC Research Press Web site at canjchem.nrc.ca on 18 April 2007.

J. Božlović, J.W. Bats, and J.W. Engels.[2] Institute for Organic Chemistry and Chemical Biology, Max-von-Laue-Str. 7, 60438 Frankfurt am Main, University of Frankfurt, Germany.

[1]This article is part of a Special Issue dedicated to Professor Kelvin K. Ogilvie.

[2]Corresponding author (e-mail: Joachim.Engels@chemie.uni-frankfurt.de).

Synthesis

The synthesis of fluoroindoles (which are not commercially available) was achieved very efficiently in a four-step procedure (4) as shown in Fig. 2. Methyl azidoacetate, an in-

 doi:10.1139/V07-020

Fig. 1. Synthesized fluoroindoles (4FBI, 5FBI, etc. are abbreviations for substituted fluorobenzimidazoles).

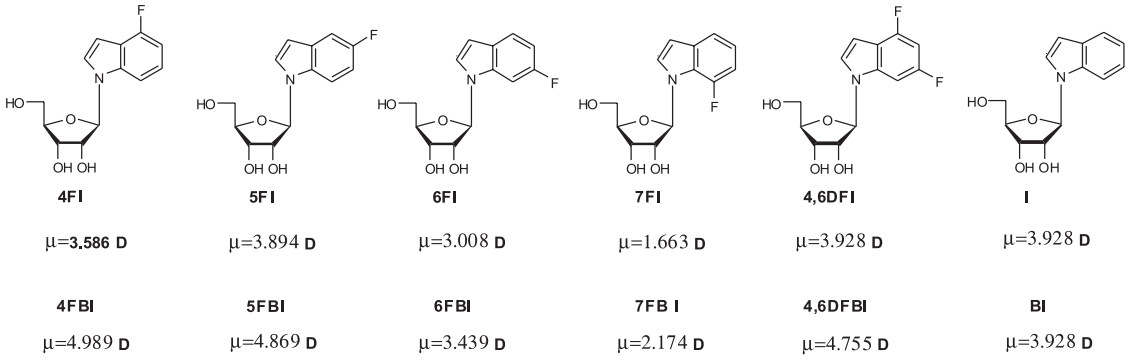
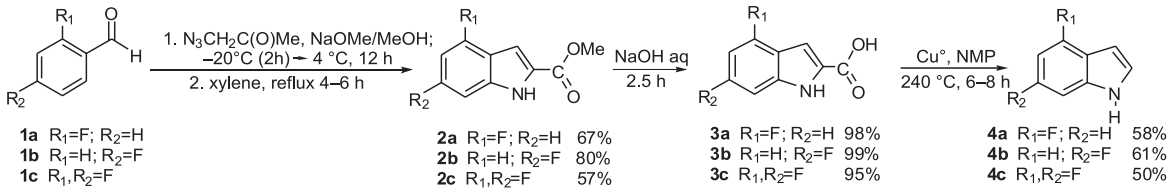


Fig. 2. Synthesis of fluoroindoles.



termediate in indole synthesis, was synthesized by a literature procedure (5). The prolonged reaction time and lower temperature improved the literature procedures (**2a**–**2c**). After hydrolysis of the methyl ester the decarboxylation followed, during which the main problem lies in the very high temperature at which the reaction occurs. Prolonging the reaction time does not lead to higher yields.

The direct synthesis of ribonucleosides was tried with 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride as the ribofuranosyl donor and a base for deprotonation of indole. Reaction conditions were varied: solvents (CH_3CN, THF, toluene), bases (NaH, TDA1–KOH), temperatures (RT to 70 °C), and reaction times (30 min to 19 h). When CH_3CN was used as a solvent and TDA1–KOH as a base, we obtained yields below 5% and separation of the obtained products was difficult to achieve (6). The Vorbrueggen method, though varying the time (2, 4, 8, and 12 h, reflux), gave no product. As can be seen, a variety of conditions and bases were tried but they did not result in a successful ribonucleoside synthesis.

As none of the direct glycosilations tried was successful, we decided to first synthesize the deoxy derivative and then the ribo derivative thereof, as shown in Fig 3. For glycosilation, we used the protected chlorodeoxyribose derivative (7). The deoxy derivative was obtained in very high yield. The key point is that the glycosilation reaction is very fast and that therefore only the β isomer is obtained (isomerization of the sugar **5** does not take place because of the fast reaction time). After deprotection, the 5′-OH is protected again with TBDPS-Cl and 3′-OH with MsCl. Deprotection of 5′-OH and elimination of OMs is accomplished in a one-step procedure. All yields reported are very good (more than 90%) except for the dihydroxilation with OsO_4 for which the yields vary from 45%–70% (based on **10a**–**10e**). However, the overall yields are between 27% and 46%. Despite the formally "long way" of synthesis, all procedures are worked out as routine and the overall yields are satisfactory.

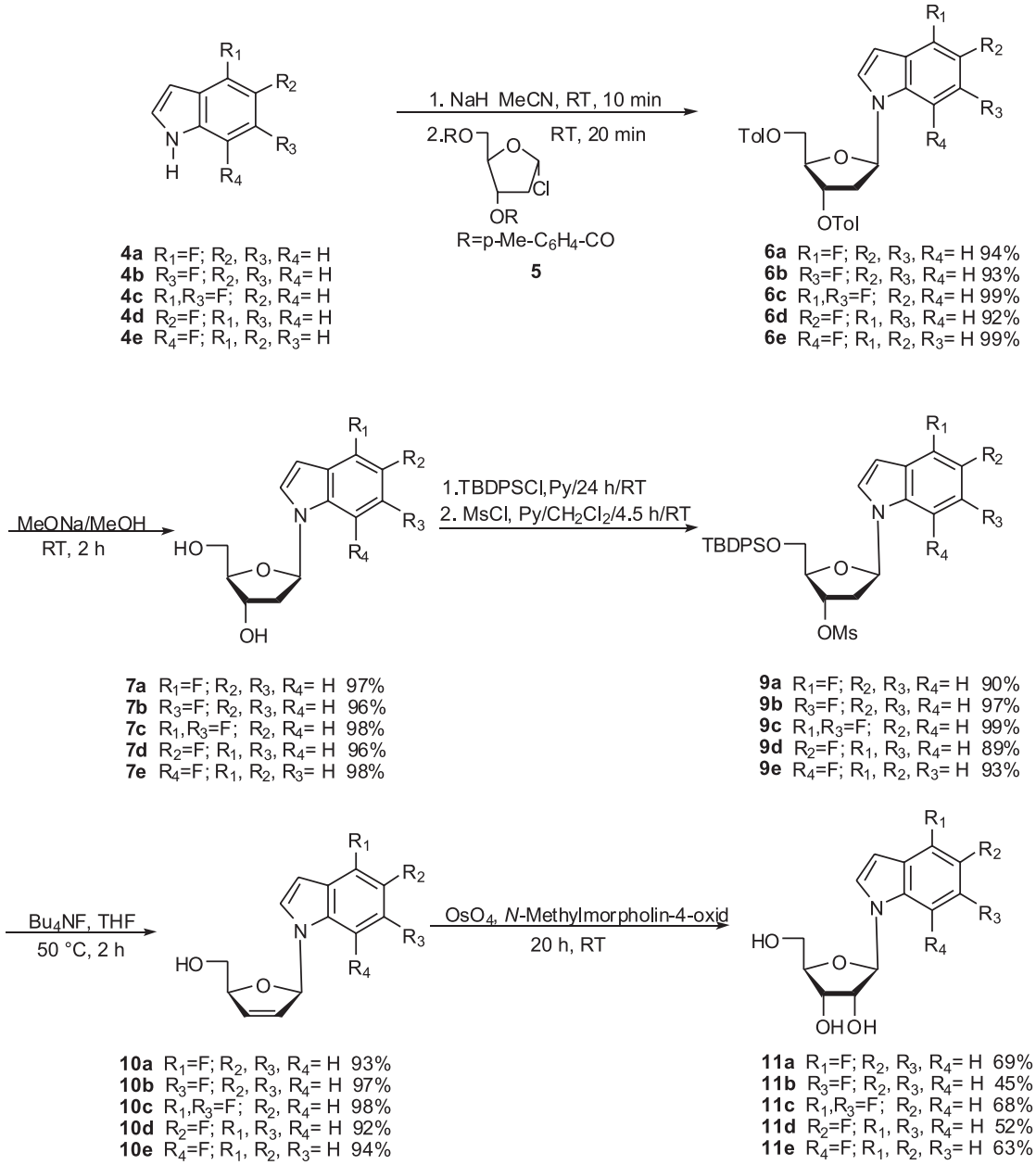
Crystal structures of fluoroindoles

The crystal structures of 5FI, 6FI, and 4,6DFI are isomorphous and have the orthorhombic space group $P2_12_12_1$. The structures 4FI and 7FI are monoclinic with space groups $P2_1$ and $C2$, respectively. The five-membered furanose ring has a conformation between a *C*2-exo, *C*3-endo half chair, and a *C*3-endo envelope in four of the five compounds. A *C*2-endo, *C*3-exo half chair is found for 4FI. The fluoroindole groups are essentially planar and adopt anti orientations about the glycosyl bond. The O4′–C1′–N–C7 torsion angles are –99.8, –86.2, –79.8, –171.0, and –85.8 ° for 4FI, 5FI, 6FI, 7FI, and 4,6DFI, respectively. The outlying value for 7FI may result from an intramolecular C–H···F interaction between the 7-fluoro atom and the H2′ atom (distance F···H = 2.51 Å).

The crystal packings of all five structures show layers of molecules connected by intermolecular O–H···O hydrogen bonds. The packing in 4FI is shown in Fig. 4. Layers of molecules are found parallel to the [0 0 1] plane. Molecules within each layer are not only connected by hydrogen bonding between the hydroxyl groups but are also connected by weak C–H···O and C(furanose)–H···π(indole) interactions. There is no hydrogen bonding between neighboring layers. Instead, the indole groups of neighboring layers are connected by C(indole)–H···π(indole) contacts. The shortest H···C distance is 2.79 Å The 4-fluoro atom is of minor importance for the crystal stabilization. The shortest intermolecular H···F distance is 2.69 Å.

The crystal packing in 6FI is shown in Fig. 5. A similar packing is found in the isomorphous 5FI and 4,6DFI structures. Again, layers of molecules are found parallel to the [0 0 1] plane. Molecules within a layer are connected by three O–H···O hydrogen bonds, three weak intermolecular C–H···O contacts, and a weak intermolecular C(furanosyl)–H···π(indole) interaction. The fluoroindole units of neighboring layers show intermolecular C(indole)–H···F contacts

Fig. 3. Efficient synthesis of fluoroindole nucleosides.



with H···F distances of 2.40 Å and C–H–F angles of 155 °. There also is an additional C(indole)–H···π(indole) interaction with H···C distances of 2.71 and 2.72 Å.

In the isomorphous 5FI structure, a similar C(indole)–H···F contact occurs with a H···F distance of 2.46 Å and a C–H–F angle of 146 °. The isomorphism of the 5-fluoro and the 6-fluoro compounds may seem surprising but can easily be understood as a C(6)–F(6)···H(5)–C(5) contact occurring in 6FI and a related C(6)–H(6)···F(5)–C(5) contact in 5FI, with only the fluorine position reversed. A similar packing is also observed for 4,6DFI. Here, only the 6-fluoro atom is involved in an intermolecular C–H···F contact (H···F distance 2.39 Å, C–H–F angle 155 °), while the 4-fluoro atom is not involved in any short contacts.

A somewhat different packing pattern is found for 7FI. This structure contains bilayers of molecules parallel to the [0 0 1] plane. The molecules in each bilayer are connected by three intermolecular O–H···O hydrogen bonds, a weak intermolecular C(furanose)–H···π(indole) interaction, and an intermolecular C–H···F contact (H···F distance 2.30 Å, C–H–F angle 124 °). Neighboring bilayers are connected by C(indole)–H···π(indole) contacts only, with a shortest H···C distance of 2.84 Å.

Thus the conclusion of this work is that all five compounds form two-dimensional networks of hydrogen-bonded molecules. The indole units point away from the layers. The packing between the layers is governed by a competition of weak C–H···π and C–H···F interactions and thus depend on the substitution pattern of the fluorine containing indole units. Similar results were found for a series of fluorine-substituted 1-(β-D-ribofuranosyl)phenyls (8).

Unfortunately it is impossible to compare in depth the

Fig. 4. Crystal packing of 4-fluoro-1-(β-D-ribofuranosyl)indole.

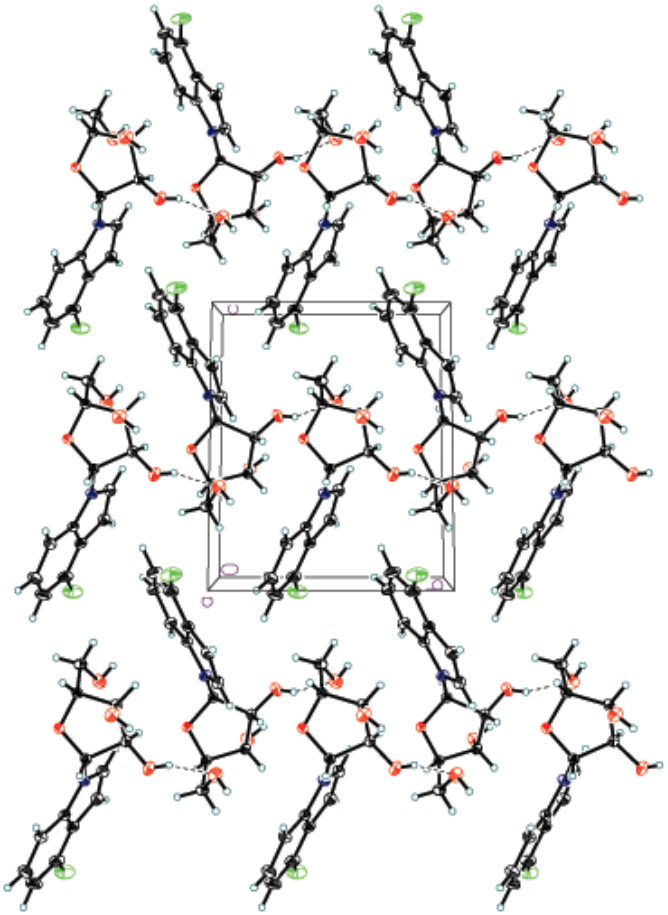
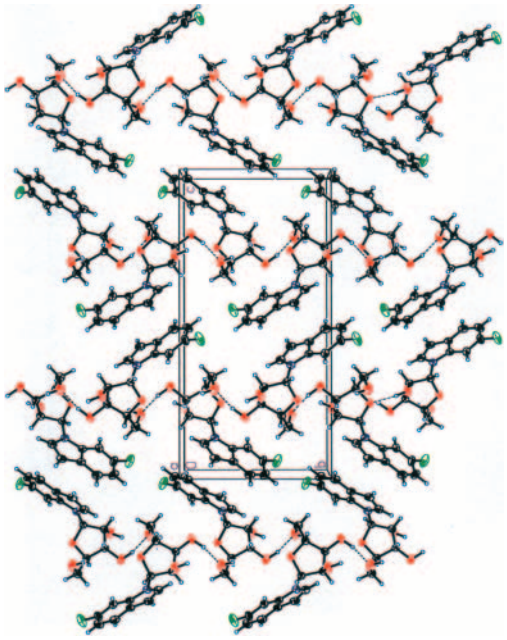


Fig. 5. Crystal packing of 6-fluoro-1-(β-D-ribofuranosyl)indole.



crystal structures of fluoroindoles and fluorobenzimidazoles because the only known crystal structure of fluorobenzimidazole is that of 1′,2′-dideoxy,3′,5′-dihydroxy-1′-(4-fluoro-6-methylbenzimidazole)-β-D-ribofuranose. There are, however, some similarities between fluoroindoles and this compound. Intermolecular C–H···F contacts also play a dominant role in the packing of the the crystal structure of 1′,2′-dideoxy,3′,5′-dihydroxy-1′-(4-fluoro-6-methylbenzimidazole)-β-D-ribofuranose (9). The molecules in this structure are connected into bilayers by O–H···O, O–H···N, C–H···O, and C–H···N hydrogen bonds. Neighboring bilayers are connected by three different C–H···F interactions with H···F distances between 2.51 and 2.59 Å.

Experimental section

Crystal structure analyses of 4FI, 5FI, 6FI, 7FI, and 4,6DFI

The compounds were crystallized from methanol or methanol–water. Single crystals were measured on a Siemens SMART 1K CCD diffractometer with Mo Kα radiation. Details of the measurements and the crystal data are given in Table 1. Empirical absorption corrections were made. Equivalent reflections, including Friedel opposites, were merged. The structures were determined by direct methods and refined by least-squares against all measured F^2 values. H atoms were either taken from a difference synthesis and refined or they were geometrically positioned and were constrained. Crystallographic data in cif format for the compounds 4FI, 5FI, 6FI, 7FI, and 4,6DFI can be found in the Supplementary Data.[3]

General

The anhydrous solvents, for example, methanol, acetonitrile, pyridine, CH_2Cl_2, and THF, were obtained from Fluka and used without further purification. Flash column chromatography was performed on (FC) silica gel (40–63 μm) from Merck, TLC on silica gel 60 F_{254} plates from Merck, NMR on a Bruker-AM250 and Bruker-AMX400 (^{1}H, ^{13}C, ^{19}F) spectrometers (δ in ppm, J in Hz), MS on a PerSeptive Biosystems MALDI-TOF spectrometer and Fisons VG platform II (ESI = electrospray-ionization).

General procedure for the preparation of methyl indole-2-carboxylates (8a–8c)

To a solution of MeONa (28.6 mL, 5.4 mol/L MeONa in MeOH) in MeOH (60ml) at –20 °C was added a solution of benzaldehyde (33 mmol) and methyl azidoacetate (135 mmol) in MeOH (34 mL) dropwise over 30 min. The mixture was stirred for 3 h at –20 °C and overnight at 4 °C. The heterogenous mixture was then poured over ice, allowed

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5154. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC numbers 631201, 631202, 631203, 631204, and 631205 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 1. Crystal data for compounds 4FI, 5FI, 6FI, 7FI, and 4,6DFI.

Compound	4FI	5FI	6FI	7FI	4,6DFI
Empirical formula	$C_{13}H_{14}FNO_4$	$C_{13}H_{14}FNO_4$	$C_{13}H_{14}FNO_4$	$C_{13}H_{14}FNO_4$	$C_{13}H_{13}F_2NO_4$
Formula weight	267.25	267.25	267.25	267.25	285.24
T (K)	157(2)	158(2)	159(2)	166(2)	155(2)
Wavelenght (Å)	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Orthorombic	Orthorhombic	Monoclinic	Orthorombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$C2$	$P2_12_12_1$
a (Å)	6.7842(16)	5.8582(8)	5.8244(11)	15.078(4)	5.7950(12)
b (Å)	8.512(2)	10.001(2)	10.0373(18)	4.6615(10)	10.143(3)
c (Å)	10.359(2)	20.029(3)	20.640(4)	17.765(6)	20.863(4)
β (°)	102.390(12)	90.00	90.00	109.610(12)	90.00
Volume (Å ^{3})	584.3(2)	1173.5(3)	1206.7(4)	1176.2(6)	1226.3(5)
Z	2	4	4	4	4
D_{calcd} (g cm^{-3})	1.519	1.513	1.471	1.509	1.545
Absorption coefficient (mm^{-1})	0.123	0.122	0.119	0.122	0.134
F (000)	280	560	560	560	592
Crystal size (mm)	0.6 × 0.6 × 0.11	0.55 × 0.1 × 0.08	0.6 × 0.15 × 0.03	0.9 × 0.36 × 0.03	0.7 × 0.09 ×x 0.05
Θ range for data collection (°)	2.0–32.7	2.0–30.8	2.0–27.4	2.4–31.0	2.0–29.9
Reflections collected	10 407	19 168	11 376	9 870	19 653
Independent reflections (R_{int})	2123 (0.018)	2036 (0.071)	1529 (0.223)	1934 (0.065)	1959 (0.068)
Observed reflections ($I > 2\sigma(I)$	2043	1458	990	1456	1543
Goodness-of-fit on F^2	1.13	1.04	1.18	0.97	1.08
Final R1 [$I > 2\sigma(I$]	0.029	0.045	0.074	0.040	0.040
w $R2$ (all data)	0.079	0.092	0.155	0.089	0.090

to warm to 5–10 °C, filtered, and the precipitate was washed with water. The solid was immediately dissolved in xylenes (100 mL) and the solution was washed with brine and dried over $MgSO_4$. The resulting solution was added dropwise to a flask of xylenes (200 mL) at reflux and the solution was held at reflux until TLC indicated the reaction was complete (3–6 h). The mixture was concentrated to dryness. The residue was purified by flash column chromatography (CH_2Cl_2).

Methyl-4-fluorindol-carboxylate (2a)

This compound was obtained from **1a** as a white solid in 66.7% yield. TLC (CH_2Cl_2). R_f 0.63. ^{1}H NMR (250 MHz, DMSO-d_6, ppm) δ: 12.29 (s, 1H, NH), 7.35 (m, 2H, 6H, 7H), 7.17 (s, 1H, 3H), 6.86 (m, 1H, 5H), 3.92 (s, 3H, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 163.18 (C=O), 162.11 (C2), 159.38 (C6), 138.03 (C8), 128.55 (C9), 124. 36 (C7), 110.43 (C5), 108.75 (C3), 98.60 (C4), 52.47 (OCH_3). ESI-MS: 193.8 $[M + H]^+$.

Methyl-6-fluorindol-carboxylate (2b)

This compound was obtained from **1b** as a white solid in 80% yield. TLC (CH_2Cl_2). R_f 0.68. ^{1}H NMR (250 MHz, DMSO-d_6, ppm) δ: 11.99 (s, 1H, NH,), 7.69 (dd, 1H, J = 5.52 Hz, J = 8.82 Hz, 7H), 7.16 (m, 2H, 3H, 4H), 6.96 (m, 1H, 5H), 3.87 (s, 3H, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6, ppm) δ: 163.18 (C=O), 162.11 (C2), 159.38 (C6), 138.03 (C8), 128.55 (C9), 124. 36 (C7), 110.43 (C5), 108.75 (C3), 98.60 (C4), 52.47 (OCH_3). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –117,22 (m, 1F, 6F). ESI-MS: 191.6 $[M + H]^+$.

Methyl-4,6-difluorindol-carboxylate (2c)

This compound was obtained from **1c** as a white solid in 73% yield. TLC (CH_2Cl_2). R_f 0.49. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 12.36 (s, 1H, NH), 7.16 (m, 1H, 7H), 7.04 (m, 1H, 3H), 6.92 (ddd, 1H, J = 2.0 Hz, J' = 8.3 Hz, J'' = 8.3 Hz, 5H), 3.89 (s, 3H, OCH_3). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –116.65 (m, 1F, 6F), –114.20 (m, 1F, 4F). ESI-MS: 209.6 $[M - H]^-$. EI anal. calcd.: C 56.88, H 3.34, N 6.63; found: C 57.04, H 3.41, N 6.48.

General procedure for the preparation of indole-2-carboxylic acids (9a–9c)

Methyl indole-2-carboxylates (21.6 mmol) were added to a solution of aq. 2 mol/L NaOH (350 mL). The mixture was stirred at reflux for 1–2 h. The solution was cooled and neutralized with concd. HCl. The resulting precipitate was collected by filtration, washed with water, and dried under vacuum to obtain indole-2-carboxylic acid.

4-Fluorindole-2-carboxylic acid (3a)

This compound was obtained from **2a** as a white solid in 98% yield. ^{1}H NMR (250 MHz, DMSO-d_6, ppm) δ: 12.09 (s, 1H, NH), 7.29–7.19 (m, 2H, 6H, 7H), 7.95 (m, 1H, 3H), 3.39 (bs, 1H, COOH). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –120.77 (m, 1F, 4F). ESI-MS: 177.6 $[M - H]^-$.

6-Fluorindole-2-carboxylic acid (3b)

This compound was obtained from **2b** as a white solid in 99% yield. TLC (CH_2Cl_2–MeOH 95:5). R_f 0.33. ^{1}H NMR (250 MHz, DMSO-d_6, ppm) δ: 12.97 (bs, 1H, COOH), 11.80 (s, 1H, NH), 7.66 (dd, 1H, J = 8.8 Hz, J' = 5.5 Hz, 4H), 7.12 (m, 2H, 3H, 7H), 6.51 (ddd, 1H, J = 8.8 Hz, J' = 9.7 Hz, J'' = 2.5 Hz, 5H). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –117.86 (m, 1F, 6F). ESI-MS: 179.2 $[M + H]^+$.

4,6-Difluorindole-2-carboxylic acid (3c)

This compound was obtained from **2c** as a white solid in 99% yield. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.25 (bs, 1H, NH), 7.10 (s, 1H, 3H), 7.02 (dd, 1H, J = 9.4 Hz, J = 1.3 Hz, 7H), 6.91 (m, 1H, 5H), 3.42 (bs, 1H, COOH). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –116.91 (m, 1F, 6F), –114.82 (m, 1F, 4F). ESI-MS: 197.9 $[M + H]^+$.

General procedure for the preparation of fluorinated indoles (4a–4c)

The indole-2-carboxylic acid (12.5 mmol), copper powder (50 mmol), and *N*-methylpyrrolidinon (200 mL) were heated at reflux. A continuous stream of argon bubbled slowly through the reaction mixture via a metal tube, while maintaining reflux for 6–12 h. The mixture was cooled, filtered through Celite, and the filter cake was washed with ether. The filtrate and ether were diluted with water (500 mL) and extracted four times with ether. The organic extract was washed with water and brine, dried with $MgSO_4$, and concentrated to dryness. The residue was purified by flash column chromatography (CH_2Cl_2).

4-Fluoroindole (4a)

This compound was obtained from **3a** as white crystals in 58% yield. TLC (*n*-hexan–EtOAc 85:15). R_f 0.40. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 11.41 (bs 1H, NH), 7.39 (m, 1H, 2H), 7.23 (m, 1H, 7H), 7.05 (m, 1H, 6H), 6.76 (m, 1H, 5H), 6.49 (d, 1H, 3H). ESI-MS: 133.7 $[M - H]^-$. EI anal. calcd.: C 71.10, H 4.48, N 10.36; found: C 71.38, H 4.64, N 10.44.

6-Fluoroindole (4b)

This compound was obtained from **3b** as white crystals in 61% yield. TLC (*n*-hexan–EtOAc 85:15). R_f 0.38. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.12 (bs 1H, NH), 7.59 (d, 1H, J = 3.3 Hz, 2H), 7.18 (dd, 1H, J = 8.7 Hz, J' = 5.6 Hz, 4H), 7.07 (dd, 1H, J = 2.2 Hz, J' = 10.2 Hz, 7H), 6.90 (ddd, 1H, J = 8.7 Hz, J' = 2.2 Hz, J'' = 10.1 Hz, 5H), 6.54 (d, 1H, J = 3.3 Hz, 3H). ^{19}F NMR (235.4 MHz, $CDCl_3$, ppm) δ: –121.83 (m, 1F, 6F). ESI-MS: 121.8 $[M + H]^+$. EI anal. calcd.: C 71.11, H 4.44, N 10.37; found: C 71.20, H 4.42, N 10.50.

4,6-Difluoroindole (4c)

This compound was obtained from **3c** as white crystals in 50% yield. TLC (*n*-hexan–EtOAc 85:15). R_f 0.43. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.35 (d, 1H, J = 2.6 Hz, 2H), 7.04 (dd, 1H, J = 2.1 Hz, J' = 9.6 Hz, 7H), 6.77 (m, 1H, 5H), 6.45 (d, 1H, J = 2.0 Hz, 3H), 3.46 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ: 159.60 (C4), 157.22 (C6), 137.85 (C5), 126.67 (C8), 122.98 (C3), 116.78 (C9), 109.91 (C7), 97.32 (C2). ESI-MS: 152.2 $[M - H]^-$.

General procedure for the preparation of 1-[2′-desoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-indoles (6a–6e)

To a solution of indole (6.2 mmol) in 80 mL of CH_3CN was added NaH (9.7 mmol) at room temperature (RT). The resulting solution was stirred at RT for 10 min. 3,5-Bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl-α-chloride (7.4 mmol) was then added and stirring was continued for 20 min. The reaction was quenched by adding Dowex-80 and the resulting mixture was filtered and concentrated to dryness. The residue was purified by flash column chromatography (hexane–EtOAc 85:15).

1-[2′-Desoxy-3′,5′-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-4-fluoroindole (6a)

This compound was obtained from **4c** as a white foam in 94% yield. TLC (hexane–EtOAc 85:15). R_f 0.29. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.95 (m, 4H, H_{Ar}), 7.45 (d, 1H, J = 3.4 Hz, 2H), 7.32–7.06 (m, 6H, H_{Ar}), 6.82 (m, 1H, 5H), 6.66 (d, 1H, J = 3.4 Hz, 3H), 6.45 (pt, 1H, J = 5.6 Hz, J' = 6.7 Hz, 1′H), 5.72 (m, 1H, 3′H), 4.76 (m, 2H, 5′H), 4.62 (m, 1H, 4′H), 2.89 (m, 1H, 2′H_β), 2.70 (m, 1H, 2′H_α), 2.47 (s, 3H, Ar-CH_3), 2.44 (s, 3H, Ar-CH_3). ^{19}F NMR (235.4 MHz, $CDCl_3$, ppm) δ: –121,79 (m, 1F, 4F). ESI-MS: 510.0 $[M + Na]^+$. EI anal. calc.: C 71.46, H 5.34, N 2.87; found: C 71.19, H 5.49, N 3.03.

1-[2′-Desoxy-3′,5′-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-6-fluoroindole (6b)

This compound was obtained from **4b** as a white foam in 94% yield. TLC (hexane–EtOAc 85:15). R_f 0.30. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.05 (d, 2H, J = 8.2 Hz, *o*-Tol-H), 7.96 (d, 2H, J = 8.2 Hz, *o′*-Tol-H), 7.59 (d, 1H, J = 3.3 Hz, 2H), 7.37 (dd, 1H, J = 10.2 Hz, J' = 2.1 Hz, 7H), 7.30 (d, 2H, J = 8.0 Hz, *m*-Tol-H), 7.26 (d, 2H, J = 8.0 Hz, *m′*-Tol-H), 6.93 (ddd, 1H, J = 8.8 Hz, J' = 2.1 Hz, J'' = 10.1 Hz, 5H), 6.59 (d, 1H, J = 3.3 Hz, 3H), 6.41 (pt, 1H, $J_{1'H2'H\beta}$ = 6.0 Hz, $J_{1'H,\,2'H\alpha}$ = 7.2 Hz, 1′H), 5.74 (m, 1H, 3′H), 4.67 (m, 2H, 5′H), 4.61 (m, 1H, 4′H), 2.88 (m, 1H, 2′H_β), 2.69 (m, 1H, 2′H_α), 2.49 (s, 3H, Ar-CH_3), 2.45 (s, 3H, Ar-CH_3). ESI-MS: 488.8 $[M + H]^+$. EI anal. calcd.: C 71.46, H 5.34, N 2.87; found C 71.42, H 5.53, N 3.08.

1-[2′-Desoxy-3′,5′-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-4,6-difluoroindole (6c)

This compound was obtained from **4c** as a white foam in 99% yield. TLC (hexane–EtOAc 85:15). R_f 0.33. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.00 (d, 2H, J = 8.2 Hz, *o*-Tol-H), 7.86 (d, 2H, J = 8.2 Hz, *o-′*Tol-H), 7.63 (d, 1H, J = 3.5 Hz, 2H), 7.53 (dd, 1H, J = 9.6 Hz, J' = 1.7 Hz, 7H), 7.50 (d, 2H, J = 1.6 Hz, *m*-Tol-H), 7.37 (d, 2H, J = 8.2 Hz, *m′*-Tol-H), (ddd, 1H, J = 1.7 Hz, J' = 9.4 Hz, J'' = 9.4 Hz, 5H), 6.59 (m, 2H, 1′H, 3H), 6.12 (m, 1H, 4′H), 4.55 (m, 2H, 3′H, 5′H), 2.94 (m, 1H, 2′H_β), 2.70 (m, 1H, 2′H_α), 2.41 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –119.00 (m, 1F, 6F), –118.01 (m, 1F, 4F). ESI-MS: 527.9 $[M + Na]^+$.

1-[2′-Desoxy-3′,5′-bis-O-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-5-fluoroindole (6d)

This compound was obtained from **4c** as a white foam in 92% yield. TLC (hexane–EtOAc 85:15). R_f 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.00 (d, 2H, J = 8.0 Hz, Tol-H), 7.91 (d, 2H, J = 8.0 Hz, Tol-H), 7.86 (m, 2H, H_{Ar}), 7.37 (m, 5H, H_{Ar}), 6.92 (ddd, 1H, J = 8.9 Hz, J = 11.0 Hz, J = 2.1 Hz, 6H), 6.59 (pt, 1H, $J_{1'H2'H\beta}$ = 6.1 Hz, $J_{1'H,2'H\alpha}$ = 6.8 Hz, 1′H), 6.53 (d, 1H, J = 3.1 Hz, 2H), 5.71 (m, 1H, 3′H), 4.61 (m, 1H, 4′H), 4.52 (m, 2H, 5′H), 2.95 (m, 1H, 2′H_β), 2.70 (m, 1H, 2′H_α), 2.46 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Ar-CH_3). ^{19}F NMR (235.4 MHz, $CDCl_3$, ppm) δ: –124.11 (m, 1F, 5F). ESI-MS: 509.8 [M + Na]$^+$. EI anal. calcd.: C 71.45, H 5.38, N 2.87, found: C 71.22, H 5.50, N 2.65.

1-[2′-Desoxy-3′,5′-bis*-O-*(4-methylbenzoyl)*-β-*D*-erythro-*pentofuranosyl]-7-fluoroindole (6e)

This compound was obtained from **4b** as a white foam in 99% yield. TLC (hexane–EtOAc 85:15). R_f 0.39. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.96 (m, 2H, H_{Ar}), 7.86 (m, 2H, H_{Ar}), 7.69 (d, 1H, J = 3.3 Hz, 2H), 7.43–7.30 (m, 5H, H_{Ar}), 7.04 (m, 2H, H_{Ar}), 6.70 (pt, 1H, $J_{1'H2'Hβ}$ = 6.6 Hz, $J_{1'H,2'Hα}$ = 7.6 Hz, 1′H), 6.63 (d, 1H, J = 3.3 Hz, 3H), 5.69 (m, 1H, 3′H), 4.57–4.46 (m, 3H, 5′H, 4′H), 2.96 (m, 1H, 2′$H_β$), 2.74 (m, 1H, 2′$H_α$), 2.37 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –132.04 (m, 1F, 7F). ESI-MS: 505.1 [M + NH_4]$^+$. EI anal. calcd: C 71.46, H 5.34, N 2.87; found: C 71.35, H 5.39, N 2.68.

General procedure for the preparation of 1-[2′-desoxy-β-D-*erythro*-pentofuranosyl]-indoles (7a–7e)

A mixture of 1-[2′-desoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-indole (5.8 mmol) and 6.9 mL 5.4 mol/L MeONa in MeOH (37.2 mmol) in MeOH (200 mL) was stirred at RT for 2 h. The reaction was quenched by adding Dowex-80 and the resulting mixture was filtered and concentrated with silica gel to dryness. The residue was purified by flash column chromatography (hexane–EtOAc 1:2).

1-(2′-Desoxy*-β-*D*-erythro-*pentofuranosyl)-4-fluoroindole (7a)

This compound was obtained from **6a** as a white solid in 97% yield. TLC (CH_2Cl_2–MeOH 9:1). R_f 0.57. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.64 (d, 1H, J = 3.4 Hz, 2H), 7.43 (d, 1H, J = 8.2 Hz, 7H), 7.12 (m, 1H, 6H), 6.83 (m, 1H, 5H), 6.57 (d, 1H, J = 3.4 Hz, 3H), 6.37 (pt, 1H, $J_{1'H,2'Hβ}$ = 6.2 Hz, $J_{1'H,2'Hα}$ = 7.6 Hz, 1′H), 5.29 (d, 1H, J = 4.1 Hz, 3′OH), 4.89 (t, 1H, J = 5.4 Hz, 5′OH), 4.35 (m, 1H, 3′H), 3.82 (m, 1H, 4′H), 3.53 (m, 2H, 5′H), 2.47 (m, 1H, 2′$H_β$), 2.41 (m, 1H, 2$H_α$). ^{13}C NMR (400 MHz, DMSO-d_6, ppm) δ: 138.28 (d, J = 44.8 Hz, C4), 125.92 (C2), 122.21 (C6), 119.15 (C_{Ar}), 117.05 (C_{Ar}), 106.96 (C7), 104.33 (C5), 99.13 (C3), 87.08 (C4′), 84.71 (C1′), 70.64 (C3′), 61.76 (C5′), 40.13 (C2′). ESI-MS: 252.0 [M + H]$^+$. EI anal. calcd.: C 62.14, H 5.62, N 5.57; found: C 62.33, H 5.80, N 5.35.

1-(2′-Desoxy*-β-*D*-erythro-pentofuranosyl)-6-fluoroindole (7b)

This compound was obtained from **6b** as a white solid in 96% yield. TLC (CH_2Cl_2–MeOH 9:1). R_f 0.57. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.59 (d, 1H, J = 3.3 Hz, 2H), 7.52 (dd, 1H, J = 8.7 Hz, J' = 5.6 Hz, 4H), 7.47 (m, 1H, 7H), 6.90 (ddd, 1H, J = 8.7 Hz, J' = 2.2 Hz, J'' = 10.1 Hz, 5H), 6.51 (d, 1H, J = 3.3 Hz, 3H), 6.33 (pt, 1H, $J_{1'H,2'Hβ}$ = 6.4 Hz, $J_{1'H,2'Hα}$ = 7.2 Hz, 1′H), 5.26 (d, 1H, J = 4.2 Hz, 3′OH), 4.89 (t, 1H, J = 5.3 Hz, 5′OH), 4.35 (m, 1H, 3′H), 3.81 (m, 1H, 4′H), 3.53 (m, 2H, 5′H), 2.47 (m, 1H, 2′$H_β$), 2.21 (m, 1H, 2$H_α$). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –120.84 (m, 1F, 6F). ESI-MS: 249.9 [M – H]$^-$.

1-(2′-Desoxy*-β-*D*-erythro-*pentofuranosyl)-4,6-difluoroindole (7c)

This compound was obtained from **6c** as a white solid in 98% yield. TLC (hexane–EtOAc 1:2). R_f 0.17. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.56–7.29 (m, 12H, H_{Ar}), 6.86 (ddd, 1H, J = 1.9 Hz, J' = 10.3 Hz, J'' = 10.2 Hz, 5H), 6.47 (d, 1H, J = 3.4 Hz, 3H), 6.34 (pt, 1H, $J_{1'H,2'Hβ}$ = 6.4 Hz, $J_{1'H,2'Hα}$ = 6.5 Hz, 1′H), 5.35 (d, 1H, J = 4.6 Hz, 3′OH), 4.43 (m, 1H, 3′H), 3.89 (m, 1H, 4′H), 3.72 (m, 2H, 5′H), 2.49 (m, 1H, 2′$H_β$), 2.30 (m, 1H, 2′$H_α$), 2.05 (s, 9H, *t*-Bu). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ: 155.7 (d, J = 50.6 Hz, C4), 154.8 (d, J = 62.2 Hz, C6), 141.5 (C8), 137.5 (C_{Ar}), 135.8 (C_{Ar}), 135.6 (C_{Ar}), 135.2 (C_{Ar}), 133.0 (C_{Ar}), 132.2 (C_{Ar}), 129.8 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.5 (C_{Ar}), 126.9 (C2), 111.2 (C9), 103.1 (C3), 95.7 (C5), 93.6 (C7), 83.5 (C1′), 83.3 (C4′), 65.3 (C3′), 64.2 (C5′), 36.0 (C2′), 25.73 (Si$C(CH_3)_3$), 20.5 (SiC(CH_3)$_3$). 19.5 (SiC(CH_3)$_3$), 14.5 (SiC(CH_3)$_3$). ESI-MS: 505.8 [M – H]$^-$.

1-(2′-Desoxy*-β-*D*-erythro-*pentofuranosyl)-5-fluoroindole (7d)

This compound was obtained from **6d** as a white foam in 96% yield. TLC (CH_2Cl_2–MeOH 9:1). R_f 0.56. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.90 (d, 1H, J = 3.2 Hz, 2H), 7.71 (m, 1H, 7H), 7.35 (m, 1H, 4H), 7.03 (ddd, 1H, J = 8.7 Hz, J' = 2.1Hz, J = 10.2 Hz, 6H), 6.54 (d, 1H, J = 3.2 Hz, 3H), 6.40 (pt, 1H, $J_{1'H,2'Hβ}$ = 6.3 Hz, $J_{1'H,2'Hα}$ = 6.9 Hz, 1′H), 5.32 (d, 1H, J = 4.1 Hz, 3′OH), 4.92 (t, 1H, J = 5.2 Hz, 5′OH), 4.40 (m, 1H, 3′H), 3.86 (m, 1H, 4′H), 3.57 (m, 2H, 5′H), 2.57 (m, 1H, 2′$H_β$), 2.28 (m, 1H, 2$H_α$). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –124.53 (m, 1F, 5F). ESI-MS: 249.8 [M – H]$^-$. EI anal. calcd: C 62.14, H 5.62, N 5.57; found: C 62.32, H 5.78, N 5.45.

1-(2′-Desoxy*-β-*D*-erythro-*pentofuranosyl)-7-fluoroindole (7e)

This compound was obtained from **6d** as a white foam in 98% yield. TLC (CH_2Cl_2–MeOH 9:1). R_f 0.63. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 7.73 (d, 1H, J = 3.2 Hz, 2H), 7.40 (m, 1H, H_{Ar}), 6.97 (m, 2H, H_{Ar}), 6.51 (m, 2H, 3H, 1′H), 5.31 (d, 1H, J = 4.2 Hz, 3′OH), 4.85 (t, 1H, J = 5.6 Hz, 5′OH), 4.31 (m, 1H, 3′H), 3.72 (m, 1H, 4′H), 3.53 (m, 2H, 5′H), 2.40 (m, 1H, 2′$H_β$), 2.37 (m, 1H, 2$H_α$). ^{13}C NMR (300 MHz, DMSO-d_6, ppm) δ: 132.50 (d, J = 45.0 Hz, C7), 132.40 (C2), 126.42 (C_{Ar}), 123.05 (C_{Ar}), 122.93 (C_{Ar}), 119.97 (C_{Ar}), 119.80 (C_{Ar}), 116.80 (C_{Ar}), 87.10 (C4′), 86.07 (C1′), 70.71 (C3′), 61.83 (C5′), 60.47 (C2′). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –132.23 (m, 1F, 7F). ESI-MS: 250.0 [M – H]$^-$.

General procedure for the preparation of 1-(2′-desoxy-5′-*O*-*tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-indoles (13a–13f)

To a solution of 1-[2′-desoxy-3′,5′-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-indole (3.75 mmol) in pyridine (20 mL) at 0 °C was added dropwise *tert*-butyldiphenylsilylchloride (4.3 mmol) in 30 min. The mixture was stirred at RT for 24 h and concentrated with silica gel to dryness. The residue was purified by flash column chromatography (hexane–EtOAc 4:1).

1-(2′-Desoxy-5′-*O*-*tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-4-fluoroindole (8a)

This compound was obtained from **7a** as a white solid in 87% yield. TLC (CH_2Cl_2–MeOH 99:1). R_f 0.51. ^{1}H NMR (400 MHz, DMSO-d_6 ppm) δ 7.59 (m, 4H, H_{Ar}), 7.52 (d, 1H, J = 3.4 Hz, 2H), 7.39 (m, 13H, H_{Ar}), 7.08 (m, 1H, 6H), 6.83 (m, 1H, 5H), 6.50 (d, 1H, J = 3.4 Hz, 3H), 6.41 (pt, 1H,

$J_{1'H,H\beta}$ = 6.6 Hz, $J_{1'H,H\alpha}$ = 7.9 Hz, 1′H), 5.40 (d, 1H, *J* = 4.5 Hz, 3′OH), 4.48 (m, 1H, 3H), 3.93 (m, 1H, 4′H), 3.72 (m, 2H, 5′H), 2.53 (m, 1H, 2′H_β), 2.32 (m, 1H, 2′H_α), 0.98 (s, 9H, *t*-Bu. ^{19}F-NMR (235.4 MHz, DMSO-d_6, ppm) δ –122.47 (m, 1F, 4F); ESI-MS: 490.2 $[M + H]^+$.

1-(2′-Desoxy-5′-*O-tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-6-fluorindole (8b)

This compound was obtained from **7b** as a white solid in 85% yield. TLC (*n*-hexan–EtOAc 4:1). R_f 0.20. ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 7.65–7.15 (m, 14H, H_{Ar}), 6.82 (ddd, 1H, *J* = 8.7 Hz, *J′* = 2.2 Hz, *J″* = 10.1 Hz, 5H), 6.43 (d, 1H, *J* = 3.2 Hz, 3H), 6.20 (pt, 1H, $J_{1'H,H\beta}$ = 6.3 Hz, $J_{1'H,H\alpha}$ = 7.3 Hz 1′H), 5.25 (d, 1H, *J* = 4.1 Hz, 3′OH), 4.65 (m, 1H, 3H), 3.97 (m, 1H, 4′H), 3.78 (m, 2H, 5′H), 2.57 (m, 1H, 2′H_β), 2.31 (m, 1H, 2′H_α), 1.02 (s, 9H, *t*-Bu). ^{19}F NMR (235.4 MHz, DMSO-d_6, ppm) δ: –120.74 (m, 1F, 6F). ESI-MS: 490.2 $[M + H]^+$.

1-(2′-Desoxy-5′-*O-tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-4,6-fluorindole (8c)

This compound was obtained from **7c** as a white solid in 88% yield. TLC (*n*-hexan–EtOAc 1:2). R_f 0.17. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.56–7.29 (m, 12H, H_{Ar}), 6.86 (ddd, 1H, *J* = 1.9 Hz, *J′* = 10.3 Hz, *J″* = 10.2 Hz, 5H), 6.47 (d, 1H, *J* = 3.4 Hz, 3H), 6.34 (pt, 1H, $J_{1'H,2'H\beta}$ = 6.4Hz, $J_{1'H,2'H\alpha}$ = 6.5 Hz, 1′H), 5.35 (d, 1H, *J* = 4.6 Hz, 3′OH), 4.43 (m, 1H, 3′H), 3.89 (m, 1H, 4′H), 3.72 (m, 2H, 5′H), 2.49 (m, 1H, 2′H_β), 2.30 (m, 1H, 2′H_α), 2.05 (s, 9H, *t*-Bu). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ: 155.7 (d, *J* = 50.6 Hz, C4), 154.8 (d, *J* = 62.2 Hz, C6), 141.5 (C8), 137.5 (C_{Ar}), 135.8 (C_{Ar}), 135.6 (C_{Ar}), 135.2 (C_{Ar}), 133.0 (C_{Ar}), 132.2 (C_{Ar}), 129.8 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.5 (C_{Ar}), 126.9 (C2), 111.2 (C9), 103.1 (C3), 95.7 (C5), 93.6 (C7), 83.5 (C1′), 83.3 (C4′), 65.3 (C3′), 64.2 (C5′), 36.0 (C2′), 25.73 (Si*C*$(CH_3)_3$), 20.5 (SiC(*C*$H_3)_3$). 19.5 (SiC(*C*$H_3)_3$), 14.5 (SiC(*C*$H_3)_3$). ESI-MS: 505.8 $[M - H]^-$.

1-(2′-Desoxy-5′-*O-tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-5-fluorindole (8d)

This compound was obtained from **7d** as a white solid in 86% yield. TLC (*n*-hexan–EtOAc 4:1). R_f 0.23. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.62 (d, 1H, *J* = 3.1 Hz, 2H), 7.50 (m, 12H, H_{Ar}), 6.95 (ddd, 1H, *J* = 8.6 Hz, *J′* = 2.1 Hz, *J″* = 10.1 Hz, 6H), 6.45 (m, 2H, 2H, 1′H), 5.44 (d, 1H, *J* = 4.2 Hz, 3′OH), 4.53 (m, 1H, 3′H), 4.05 (m, 1H, 4′H), 3.85 (m, 2H, 5′H), 2.60 (m, 1H, 2′H_β), 2.38 (m, 1H, 2′H_α), 1,04 (s, 9H, *t*-Bu). ^{19}F NMR (283.3 MHz, DMSO-d_6, ppm) δ: –124.76 (m, 1F, 5F) ESI-MS: 489.1 $[M - H]^-$.

1-(2′-Desoxy-5′-*O-tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-7-fluorindole (8e)

This compound was obtained from **7e** as a white solid in 89% yield. TCL (*n*-hexan–EtOAc 4:1). R_f 0.36. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.66 (m, 5H, H_{Ar}), 7.48–7.38 (m, 7H, H_{Ar}), 7.10–7.01 (m, 2H, H_{Ar}), 6.60 (pt, 1H, $J_{1'H,H\beta}$ = 6.3 Hz, $J_{1'H,H\alpha}$ = 7.1 Hz, 1′H), 6.55 (d, 1H, *J* = 3.1 Hz, 2H), 5.47 (d, 1H, *J* = 4.3 Hz, 3′OH), 4.50 (m, 1H, 3′H), 3.97 (m, 1H, 4′H), 3.77 (m, 2H, 5′H), 2.48 (m, 1H, 2′H_β), 2.39 (m, 1H, 2′H_α), 1.04 (s, 9H, *t*-Bu). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –132.64 (m, 1F, 7F). ESI-MS: 490.2 $[M + H]^+$. EI anal. calcd.: C 71.13, H 6.59, N 2.86; found: C 70.84, H 6.83, N 2.67.

General procedure for the preparation of 1-(2′-desoxy-5′-*O-tert*-buthyldimethylsisyl-3′-*O*-mesyl-β-D-*erythro*-pentofuranosyl)-indoles (9a–9f)

To a solution of 1-(2′-desoxy-5′-*O-tert*-buthyldiphenylsilyl-β-D-*erythro*-pentofuranosyl)-indole (3.2 mmol) in mixture of CH_2Cl_2 and pyridine (4:1, 75 mL) at 0 °C was added MsCl (64 mmol) and stirred at RT over night. After the addition of MeOH (20 mL) and further stirring for 20 min, the mixture was concentrated to dryness and coevaporated with toluene. The residue was purified by flash column chromatography (hexane–EtOAc 4:1).

1-(2′-Desoxy-5′-*O-tert-*butyldimethylsisyl-3′-O-*mesyl*-β-D-erythro-*pentofuranosyl)-4-fluorindol (9a)

This compound was obtained from **8a** as a white foam in 90% yield. TLC (hexane–EtOAc 75:25). R_f 0.51. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.74–7.12 (m, 13H, H_{Ar}), 6.82 (m, 1H, 5H), 6.59 (d, 1H, *J* = 3.3 Hz, 3H), 6.37 (pt, 1H, $J_{1'H,2'H\beta}$ = 8.6 Hz, $J_{1'H,2'H\alpha}$ = 5.5 Hz, 1′H), 5.52 (m, 1H, 3′H), 4.33 (m, 1H, 4′H), 3.88 (m, 2H, 5′H), 3.07 (s, 3H, SCH_3), 2.72 (m, 2H, 2′H), 1.12 (s, 9H, *t*-Bu). ^{19}F NMR: (235.4 MHz, $CDCl_3$, ppm) δ: –121.87 (m, 1F, 4F). ESI-MS: 568.3 $[M + H]^+$.

1-(2′-Desoxy-5′-*O-tert-*butyldimethylsilyl-3′-O-*mesyl*-β-D-erythro-*pentofuranosyl)-6-fluoroindole (9b).

This compound was obtained from **8b** as a white foam in 97% yield. TLC (hexane–EtOAc 4:1). R_f 0.30. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.69–7.20 (m, 14H, H_{Ar}), 6.93 (ddd, 1H, *J* = 8.8 Hz, *J′* = 2.3 Hz, *J″* = 9.4 Hz, 5H), 6.32 (pt, 1H, $J_{1'H,2'H\beta}$ = 5.5 Hz, $J_{1'H,2'H\alpha}$ = 3.5 Hz, 1′H), 5.53 (m, 1H, 3′H), 4.34 (m, 1H, 4′H), 3.93 (dd, 1H, *J* = 11.4 Hz, *J′* = 3.2 Hz, 5′H_α), 3.84 (dd, 1H, *J* = 4.2 Hz, *J′* = 11.4 Hz, 5′H_β), 3.10 (s, 3H, SCH_3), 2.76 (m, 1H, 2′H_β), 2.47 (m, 1H, 2′Hα), 1.14 (s, 9H, *t*-Bu). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ: 161.18 (C_{Ar}), 158.81 (C4), 136.42 (C_{Ar}), 135.58 (d, *J* = 10.6 Hz, C6), 132.48 (C_{Ar}), 129.97 (C8), 127.92 (C_{Ar}), 125.44 (C3), 124.38 (C_{Ar}), 121.69 (C9), 109.25 (C7), 96.75 (C2), 96.45 (C5), 84.87 (C1′), 83.90 (C3′), 80.27 (C4′), 76.68 (C5′), 63.38 (C2′), 38.44 (SCH_3), 26.92 (SiC(*C*$H_3)_3$), 19.24 (Si*C*$(CH_3)_3$). ESI-MS: 568.5 $[M + H]^+$.

1-(2′-Desoxy-5′-*O-tert-*butyldimethylsisyl-3′-O-*mesyl*-β-D-erythro-*pentofuranosyl)-4,6-fluorindole (9c)

This compound was obtained from **8c** as a white foam in 99% yield. TLC (*n*-hexan–EtOAc 85:15). R_f 0.16. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.60–7.33 (m, 12H, H_{Ar}), 6.92 (m, 1H, 5H), 6.54 (d, 1H, *J* = 3.4 Hz, 3H), 6.45 (pt, 1H, $J_{1'H,2'H\beta}$ = 6.3 Hz, $J_{1'H,2'H\alpha}$ = 6.4 Hz, 1′H), 5.44 (m, 1H, 3′H), 4.26 (m, 1H, 4′H), 3.81 (m, 2H, 5′H), 3.30 (s, 9H, SCH_3), 2.85 (m, 1H, 2′H_β), 2.73 (m, 1H, 2′H_α), 0.99 (s, 9H, *t*-Bu). ^{19}F NMR (235.3 MHz, DMSO-d_6, ppm) δ: –119.02 (m, 1F, 6F), –117.84 (m, 1F, 4F). ESI-MS: 505.8 $[M + H]^+$. EI anal. calcd.: C 61.52, H 5.68, N 2.39; found: C 61.35, H 5.47, N 2.43.

1-(2′-Desoxy-5′-*O-tert-*butyldimethylsisyl-3′-O-*mesyl*-β-D-erythro-*pentofuranosyl)-5-fluorindole (9d)

This compound was obtained from **8d** as a white foam in 89% yield. Yield 2.89 g (89%). TLC (*n*-hexan–EtOAc 4:1).

R_f 0.20. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.55 (m, 4H, H_{Ar}), 7.38–7.15 (m, 9H, H_{Ar}), 6.84 (m, 1H, 6H), 6.37 (d, 1H, J = 3.0 Hz, 3H), 6.24 (pt, 1H, $J_{1'H,2'H\beta}$ = 7.2 Hz, $J_{1'H,2'H\alpha}$ = 6.2 Hz, 1′H), 5.43 (m, 1H, 3′H), 4.23 (m, 1H, 4′H), 3.71 (m, 2H, 5′H), 2.98 (s, 3H, SCH_3), 2.61 (m, 2H, 2′H), 1.05 (s, 9H, *t*-Bu). ^{19}F NMR (282.3 MHz, $CDCl_3$, ppm) δ: –124.40 (m, 1F, 5F). ESI-MS: 567.9 $[M + H]^+$. EI anal. calcd.: C 63.47, H 6.04, N 2.47; found: C 63.36, H 6.20, N 2.39.

*1-(2′-Desoxy-5′-*O*-tert-buthyldimethylsisyl-3′-*O*-mesyl-β-D-erythro-pentofuranosyl)-7-fluorindole (9e)*

This compound was obtained from **8e** as a white foam in 93% yield. TLC (*n*-hexan–EtOAc 4:1). R_f = 0.36. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.64–7.59 (m, 5H, H_{Ar}), 7.49–7.31 (m, 7H, H_{Ar}), 7.10–6.98 (m, 2H, H_{Ar}), 6.61 (pt, 1H, $J_{1'H,2'H\beta}$ = 7.1 Hz, $J_{1'H,2'H\alpha}$ = 6.6 Hz, 1′H), 6.53 (m, 1H, H_{Ar}), 5.46 (m, 1H, 3′H), 4.27 (m, 1H, 4′H), 3.74 (m, 2H, 5′H), 3.30 (s, 3H, SCH_3), 2.93 (m, 1H, 2′H_β), 2.81 (m, 1H, 2′Hα), 1.00 (s, 9H, *t*-Bu). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –132.56 (m, 1F, 7F). ESI-MS: 567.9 $[M + H]^+$.

General procedure for the preparation of 1-(2′,3′-didesoxy-β-D-*glycero*-pent-2-enofuranosyl)indoles (10a–10e)

To a solution of compound 14 (2.8 mmol) in THF (50 mL) was added Bu_4NF (1 mol/L solution in THF, 10.4 mL). The mixture was stirred at 50 °C for 2 h (Ar atmosphere) and concentrated to dryness. The residue was purified by flash column chromatography (1st $CHCl_3$–MeOH 95:5; 2nd $CHCl_3$–MeOH 98:2).

1-(2′,3′-Didesoxy-β-D-glycero-pent-2-enofuranosyl)-4-fluoroindole (10a)

This compound was obtained from **9a** as a white solid in 93% yield. TLC ($CHCl_3$–MeOH 95:5). R_f 0.47. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.75 (d, 1H, J = 4.0 Hz, 2H), 7.59 (d, 1H, J = 4.6 Hz, 1′H), 7.22 (m, 2H, 6H, 7H), 6.91 (m, 1H, 5H), 6.61 (d, 1H, J = 4.0 Hz, 3H), 6.55 (m, 1H, 3′H), 6.21 (m, 1H, 2′H), 4.93 (t, 1H, J = 5.7 Hz, 5′OH), 4.87 (m, 1H, 4′H), 3.67 (m, 2H, 5′H). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –122.40 (m, 1F, 4F). ESI-MS: 233.8 $[M + H]^+$.

1-(2′,3′-Didesoxy-β-D-glycero-pent-2-enofuranosyl)-6-fluoroindole (10b)

This compound was obtained from **9b** as a white solid in 97% yield. TLC ($CHCl_3$–MeOH 95:5). R_f 0.51. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.55 (m, 2H, 2H, 7H), 7.37 (d, 1H, J = 3.4 Hz, 1′H), 7.03 (m, 1H, 4H), 6.91 (ddd, 1H, J = 8.6 Hz, J' = 2.2 Hz, J'' = 9.9 Hz, 5H), 6.49 (m, 2H, 3H, 3′H), 6.13 (m, 1H, 2′H), 4.86 (t, 1H, J = 5.6 Hz, 5′OH), 4.78 (m, 1H, 4′H), 3.52 (m, 2H, 5′H). ^{19}F NMR (250.1 MHz, DMSO-d_6, ppm) δ: –120.88 (m, 1F, 6F). ESI-MS: 233.9 [M + H]+). EI anal. calcd.: C 66.94, H 5.19, N 6.01; found: C 66.85, H 5.34, N 6.12.

1-(2′,3′-Didesoxy-β-D-glycero-pent-2-enofuranosyl)-4,6-fluoroindole (10c)

This compound was obtained from **9c** as a white solid in 99% yield. TLC ($CHCl_3$–MeOH 95:5). R_f 0.52. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.51 (dd, 1H, J = 1.8 Hz, 7H), 7.43 (d, 1H, J = 3.4 Hz, 2H), 7.03 (d, 1H, J = 1.3 Hz, 1′H), 6.89 (ddd, 1H, J = 1.8 Hz, J' = 10.3 Hz, J'' = 10.2 Hz, 5H), 6.56 (d, 1H, J = 3.4 Hz, 3H), 6.48 (m, 1H, 2′H), 6.13 (m, 1H, 2′H), 6.13 (m, 1H, 3′H), 4.87 (t, 1H, J = 5.4 Hz, 5′OH), 4.81 (m, 1H, 4′H), 3.51 (m, 2H, 5′H). ^{19}F NMR (235.4 DMSO-d_6, ppm) δ: –119.17 (m, 1F, 6F), –118.37 (m, 1F, 4F). ESI-MS: 251.9 $[M + H]^+$.

1-(2′,3′-Didesoxy-β-D-glycero-pent-2-enofuranosyl)-5-fluoroindole (10d)

This compound was obtained from **9d** as a white solid in 93% yield. TLC ($CHCl_3$–MeOH 95:5). R_f 0.46. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.70 (m, 1H, 6H), 7.42 (d, 1H, J = 3.6 Hz, 1′H), 7.33 (m, 1H, 2H), 7.03 (m, 2H, 7H, 3′H), 6.52 (m, 2H, 4H, 2′H), 6.15 (d, 1H, J = 3.1 Hz, 3H), 4.86 (t, 1H, J = 5.4 Hz, 5′OH), 4.80 (m, 1H, 4′H), 3.55 (m, 2H, 5′H). ^{19}F NMR (282.3 MHz, DMSO-d_6, ppm) δ: –124.44 (m, 1F, 5F). ESI-MS: 233.7 $[M + H]^+$. EI anal. calcd.: C 66.94, H 5.19, N 6.01; found: C 66.80, H 5.49, N 5.83.

1-(2′,3′-Didesoxy-β-D-glycero-pent-2-enofuranosyl)-7-fluoroindole (10e)

This compound was obtained from **9e** as a white solid in 93% yield. TLC ($CHCl_3$–MeOH 95:5). R_f 0.51. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.52 (m, 2H, 2H,6H), 7.40 (d, 1H, J = 3.4 Hz, 1′H), 7.03 (m, 1H, 4H), 6.91 (m, 1H, 5H), 6.50 (m, 2H, 3H,3′H), 6.13 (m, 1H, 2′H), 4.86 (t, 1H, J = 5.6 Hz, 5′OH), 4.78 (m, 1H, 4′H), 3.52 (m, 2H, 5′H). ^{19}F NMR (250.1 MHz, DMSO-d_6, ppm) δ: –120.88 (m, 1F, 6F). ESI-MS: 233.9 $[M + H]^+$. EI anal. calcd.: C 66.94, H 5.19, N 6.01; found: C 66.85, H 5.24, N 6.18.

General procedure for the preparation of 1′-desoxy-1′-(indolyl)-β-D-ribofuranose (16a–16f)

Compound 15 (4.4 mmol) and *N*-methyl-morpholine oxide (11.9 mmol) were dissolved in 50 mL of acetone–water (8:1) and OsO_4 (5.5 mL, 2.5% in 2-methyl-2-propanol) was added. The mixture was stirred at RT for 20 h, 10% $Na_2S_2O_4$ (15 mL) was then added and stirring was continued for 15 min. The mixture was treated with water (100 mL) and extraced with EtOAc (2 × 150 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by flash column chromatography (hexane–EtOAc 1:2).

1′-Desoxy-1′-(4-fluoroindolyl)-β-D-ribofuranose (11a)

This compound was obtained from **10a** as white crystals in 69% yield. TLC (CH_2Cl_2–MeOH 95:5). R_f 0.21. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.66 (d, 1H, J = 3.4 Hz, 2H), 7.42 (d, 1H, J = 8.3 Hz, 7H), 7.12 (m, 1H, 6H), 6.84 (m, 1H, 5H), 6.58 (d, 1H, J = 3.3 Hz, 3H), 5.88 (d, 1H, J = 6.1 Hz, 1′H), 5.34 (d, 1H, J = 5.4 Hz, 2′OH), 5.14 (s, 1H, 3′OH), 5.02 (t, 1H, J = 5.6 Hz, 5′OH), 4.26 (d, 1H, J = 5.0 Hz, 2′H), 4.08 (m, 1H, 3′H), 3.93 (m, 1H, 4′H), 3.61 (m, 2H, 5′H). ^{19}F NMR (250.4 MHz, DMSO-d_6, ppm) δ: –122.53 (m, 1F, 4F). ESI-MS: 265.7 $[M - H]^-$.

1′-Desoxy-1′-(6-fluoroindolyl)-β-D-ribofuranose (11b)

This compound was obtained from **10b** as white crystals in 45% yield. TLC (CH_2Cl_2–MeOH 95:5). R_f 0.21. ^{1}H NMR (250 MHz, DMSO-d_6, ppm) δ: 7.58 (d, 1H, J = 3.4 Hz, 2H), 7.53 (dd, 1H, J = 8.6 Hz, J' = 5.6 Hz, 4H), 7.46 (dd, 1H, J =

2.1 Hz, J' = 10.7 Hz, 7H), 6.91 (ddd, 1H, J = 8.6 Hz, J' = 2.1 Hz, J'' = 9.7 Hz, 5H), 6.51 (d, 1H, J = 3.4 Hz, 3H), 5.81 (d,1H, J = 6.1 Hz, 1′H), 5.30 (d, 1H, J = 6.7 Hz, 3′OH), 5.12 (d, 1H, J = 5.0 Hz, 2′OH), 5.03 (t, 1H, J = 5.3 Hz, 5′OH), 4.19 (m, 1H, 2′H), 4.08 (m, 1H, 3′H), 3.90 (m, 1H, 4′H), 3.61 (m, 2H, 5′H). ^{13}C NMR (62,9 MHz, DMSO-d_6, ppm) δ: 160.01 (C2), 135.70 (C4), 126. 58 (C7), 125.27 (C8), 121.38 (C6), 108.10 (C5), 102.16 (C9), 97.13 (C3), 89.04 (C1′), 84.88 (C4′), 73.90 (C2′), 70.21 (C3′), 61.42 (C5′), 124. 36 (C7), 110.43 (C5), 98.60 (C4), 52.47 (OCH_3). ^{19}F NMR (250.1 MHz, DMSO-d_6, ppm) δ: –120.95 (s, 1F, 6F). ESI-MS: 265.9 [M – H]$^-$. EI anal. calcd.: C 58.42, H 5.28, N 5.24; found: C 58.33, H 5.30, N 5.17.

1′-Desoxy-1′-(4,6-fluoroindolyl)-β-D-ribofuranose (11c)

This compound was obtained from **10c** as white crystals in 68% yield. TLC (hexane–EtOAc 1:2). R_f 0.15. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.65 (d, 1H, J = 3.4 Hz, 2H), 7.41 (dd, 1H, J = 1.7 Hz, J' = 10.1 Hz, 7H), 6.88 (ddd, 1H, J = 2.0 Hz, J' = 10.3 Hz, J'' = 10.3 Hz, 5H), 6.58 (d, 1H, J = 6.6 Hz, 3H), 5.82 (d, 1H, J = 6.2 Hz, 1′H), 5.34 (d, 1H, J = 6.7 Hz, 2′OH), 5.14 (d, 1H, J = 4.9 Hz, 3′OH), 5.06 (t, 1H, J = 5.3 Hz, 5′OH), 4.23 (m, 1H, 2′H), 4.07 (m, 1H, 3′H), 3.94 (m, 1H, 4′H), 3.62 (m, 2H, 5′H). ^{19}F NMR (235.2 MHz, DMSO-d_6, ppm) δ: –118.17 (m, 1F, 6F), –119.13 (m, 1F, 4F). ESI-MS: 283.8 [M + H]$^+$.

1′-Desoxy-1′-(5-fluoroindolyl)-β-D-ribofuranose (11d)

This compound was obtained from **10c** as white crystals in 52% yield. TLC (hexane–EtOAc 1:2). R_f 0.21. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.70 (d, 1H, J = 3.4 Hz, 2H), 7.40 (d, 1H, J = 8.1 Hz, 7H), 7.12 (m, 1H, 6H), 6.84 (m, 1H, 4H), 6.52 (d, 1H, J = 3.4 Hz, 3H), 5.78 (d, 1H, J = 6.2 Hz, 1′H), 5.30 (d, 1H, J = 5.4 Hz, 2′OH), 5.18 (s, 1H, 3′OH), 5.04 (t, 1H, J = 5.6 Hz, 5′OH), 4.36 (d, 1H, J = 5.0 Hz, 2′H), 4.09 (m, 1H, 3′H), 3.91 (m, 1H, 4′H), 3.62 (m, 2H, 5′H). ^{19}F NMR (250.4 MHz, DMSO-d_6, ppm) δ: –124.54 (m, 1F, 5F). ESI-MS: 265.7 [M – H]$^-$).

1′-Desoxy-1′-(7-fluoroindolyl)-β-D-ribofuranose (11e)

This compound was obtained from **10e** as white crystals in 48% yield. TLC (CH_2Cl_2–MeOH 95:5). R_f 0.22. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.72 (d, 1H, J = 3.2 Hz, 2H), 7.40 (d, 1H, J = 8.3 Hz, 4H), 7.10 (m, 1H, 6H), 6.84 (m, 1H, 5H), 6.58 (d, 1H, J = 3.2 Hz, 3H), 5.88 (d, 1H, J = 6.1 Hz, 1′H), 5.32 (d, 1H, J = 5.4 Hz, 2′OH), 5.12 (s, 1H, 3′OH), 5.01 (t, 1H, J = 5.6 Hz, 5′OH), 4.26 (d, 1H, J = 5.0 Hz, 2′H), 4.08 (m, 1H, 3′H), 3.93 (m, 1H, 4′H), 3.61 (m, 2H, 5′H). ^{19}F NMR (250.4 MHz, DMSO-d_6, ppm) δ: –122.50 (m, 1F, 7F). ESI-MS: 265.9 [M – H]$^-$).

Acknowledgement

The authors acknowledge the financial support by the Deutsche Forschungsgemeinschaft, SFB 579.

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