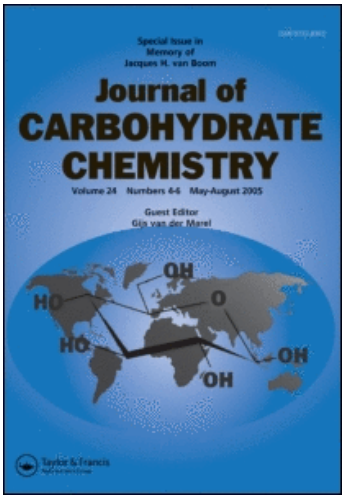

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Synthesis of Trifluoromethylated 3-(3-Pyrazolyl)indole-*N*-glycosides and their Cytotoxic Activity against Human Keratinocytes (HaCaT)

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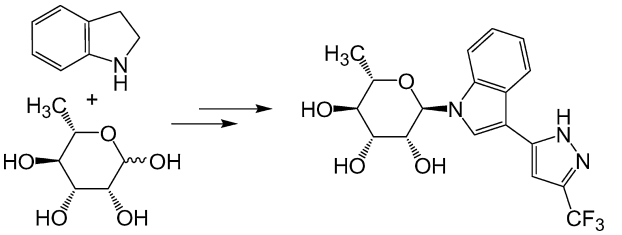
The first 3-(3-pyrazolyl)indole-*N*-glycosides were prepared starting from indole-N-glycosides by conversion with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one and following cyclization with hydrazine. The cytotoxic activity of the products against human keratinocytes (HaCaT) was studied.

Keywords Indole-*N*-glycosides; Cyclizations; *N*-heterocycles; Organofluorine compounds; Trifluoromethylated pyrazoles



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INTRODUCTION

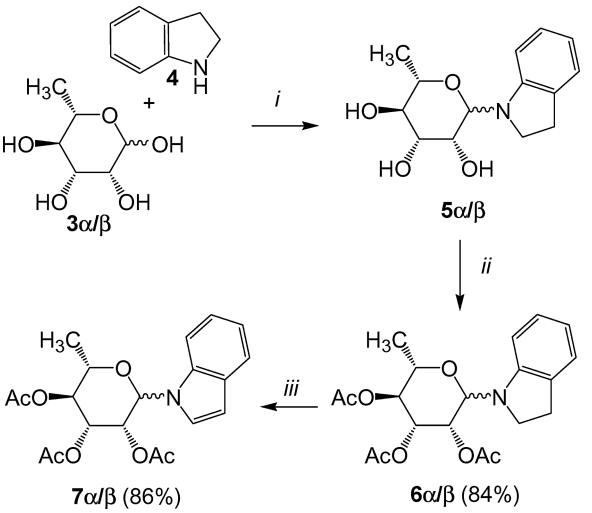
Substituted pyrazoles are an important class of compounds in the field of agricultural and medicinal chemistry because of their broad-spectrum biological activities.[1] They are used as fungicide, insecticide, herbicide, and antitumor agents.[2]

On the other hand, the trifluoromethyl (CF_3) group is of considerable importance in organic and medicinal chemistry.[3,4] While the size of the CF_3 group is comparable to the methyl group, its high electronegativity results in a much different electronic situation and a change of the reactivity, which plays an important role in drug-receptor interactions. In addition, the increased lipophilicity of CF_3-substituted molecules improves their in vivo transport. Undesirable metabolic transformations are often avoided, due to the high chemical and biological stability of the CF_3 group. Therefore, the synthesis of CF_3-substituted arenes and hetarenes plays an important role in drug discovery.[3,4] A variety of CF_3-substituted heterocycles have found applications in the clinic (e.g., triftazine, trifluorothymidine).[5,6] Fluorinated carbohydrates play an increasingly important role in organic chemistry.[7] Besides the widespread use of anomeric fluorides in glycosylation reactions, fluorinated carbohydrates play an important role in medicinal chemistry and as liquid crystals. However, the synthesis of heterocyclic *N*-glycosides, containing a CF_3 group located at the heterocyclic moiety, has only scarcely been reported in the literature so far.[8] Such compounds are of considerable pharmacological relevance as carbohydrates are known to increase the bioavailability of drugs. In this context, the presence of carbohydrate-specific carriers in the cell membrane and carbohydrate-carbohydrate recognition processes at the cell surface have to be mentioned. After the transfer of the heterocyclic *N*-glycoside through the cell membrane, the carbohydrate moiety is cleaved. Herein, we report what is, to the best of our knowledge, the first synthesis of 3-(pyrazol-3-yl)indole-*N*-glycosides and their cytotoxic activity against human keratinocytes (HaCaT).

RESULTS AND DISCUSSION

Gambaryan et al. were the first to report the catalyst-free condensation of ethyl vinylether (**1**) and trifluoroacetic anhydride (**2**) to give 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**3**).[9] Trost et al.[10] showed that this reaction follows an addition-elimination mechanism.[11] Effenberger et al. studied the reaction of vinyl ether with trichloroacetic chloride and were able to isolate the addition product (before the elimination step).[12] We have prepared 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**3**) following a modified procedure reported by Hojo und Colla.[13–15]

The reaction of **L**-rhamnose (**3*α*/*β***) with indoline (**4**) gave the *N*-rhamnoside **5*α*/*β***, which was acetylated to give **6*α*/*β*** in 84% yield (Sch. 1). The oxidation



Scheme 1: Synthesis of **7*α*/*β***. *Reagents and conditions*: (*i*) EtOH, 12 h, 20°C; (*ii*) Ac_2O, pyridine, 0°C, 12 h; (*iii*) DDQ, dioxane, 20°C, 12 h.

of the latter with DDQ gave 2′,3′,4′-tri-*O*-acetyl-**α/β**-L-rhamnopyranosyl)indole (**7*α*/*β***) as a separable mixture of anomers in 86% yield ($\beta/\alpha \sim 3{:}1$). The synthesis was carried out following a known strategy.[16,17] The synthesis of rhamnoside **7*α*/*β*** has been previously reported by Magnin.[16d] However, the authors could not unambiguously confirm the configuration at the anomeric carbon atom. We report for the first time the complete assignment of the structure and ^{13}C NMR data. In addition, the structure of anomerically pure **7*α*** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[18]

The reaction of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**3**) with indole has been reported to give 3-(*trans*-1,1,1-trifluorobut-3-en-2-on-4-yl)indole in 60% yield.[19] We have found that the reaction of **3** (1.0 equiv.) with anomerically pure indole-*N*-rhamnoside **7*β***, in the presence of $ZnCl_2$, resulted in the formation of product **8*β***, albeit in only 26% yield (Sch. 2, Table 1). The bis(indole-*N*-glycoside) **9*β***, formed by Michael-type reaction of **8*β*** with **7*β***, was isolated in 47% yield. The yield of **8*β*** could be significantly increased (62%) by using an excess of **3** (4.0 equiv.). Product **9*β*** was formed in only 22% yield. The structure of **9*β*** was confirmed by NMR spectroscopy. In the MS spectrum, the molecular ion ($m/z = 900$) and characteristic fragments (e.g., $m/z = 789$, $[CH_2C(O)CF_3]$) were detected. The reaction of **7*β*** with the CH_3-analog of **3** failed, due to the low reactivity of the latter.

The α-configured rhamnoside **8*α*** was prepared, following our optimized procedure, by reaction of **3** with **7*α*** in 71% yield (Sch. 3). Likewise, the reaction of **3** with (β-D-glucopyranosyl)indole **10*β*** afforded **11*β*** in 47% yield. The *trans*-configuration of the double bond of **8*α***, **8*β*,** and **11*β*** was proved by ^1H NMR

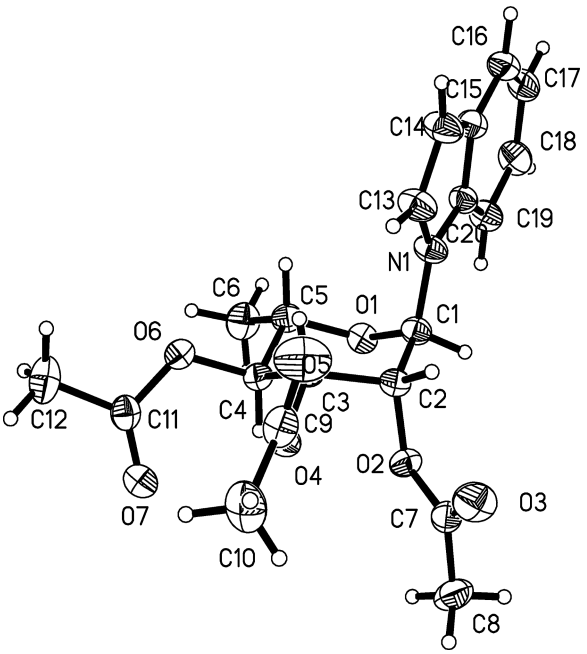


Figure 1: ORTEP-plot of **7α** (50% probability of the thermal ellipsoids).

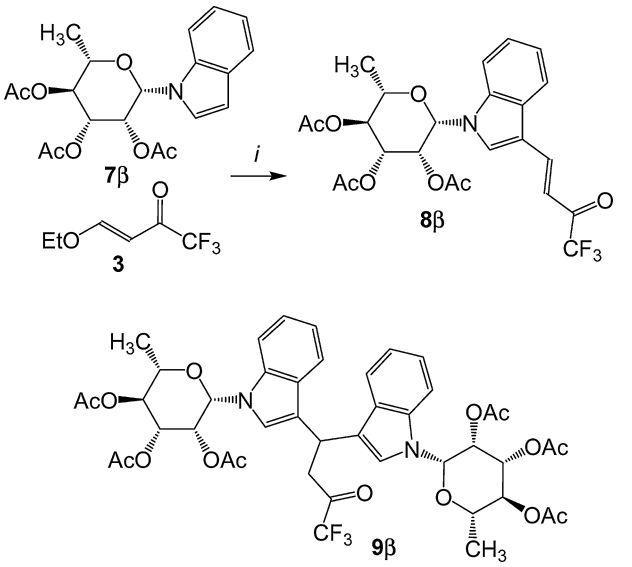
spectroscopy (the vicinal coupling constant was in the range of $^3J_{3'',4''} = 15.6$ to 15.8 Hz).

The reaction of **8β** with hydrazine hydrate afforded product **12β** as a mixture of four diastereomers (Sch. 4). The reaction of crude **12β** with a catalytic amount of *p*-toluenesulfonic acid (90°C, 1 h) gave the dihydro-*2H*-pyrazole **13β** as a mixture of two diastereomeres. The subsequent oxidation (DDQ) afforded the desired 3-(pyrazol-3-yl)indol-*N*-rhamnoside **14β** in 59% overall yield. The deprotection of **14β** failed to deliver a pure product due to separation problems. The cyclocondensation of glucoside **11β** with hydrazine failed to give a pure product. Likewise, the cyclization of **8β** with hyroxylamine proved to be unsuccessful.

Table 1: Yields of 8β and 9β

Equiv. (**3**)	Yield (**8β**) (%)[a]	Yield (**9β**) (%)[a]
1.0	26	47
4.0	62	22

[a]Yields of isolated products.

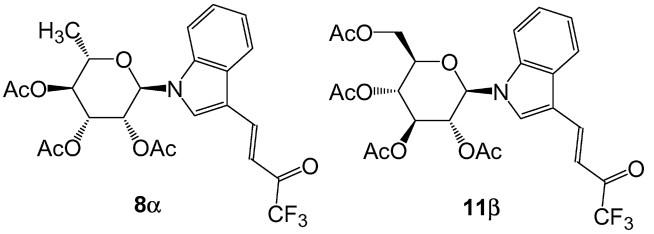


Scheme 2: Synthesis of **8*β***. *Reagents and conditions*: (*i*) $ZnCl_2$, CH_2Cl_2, 20°C, 12 h.

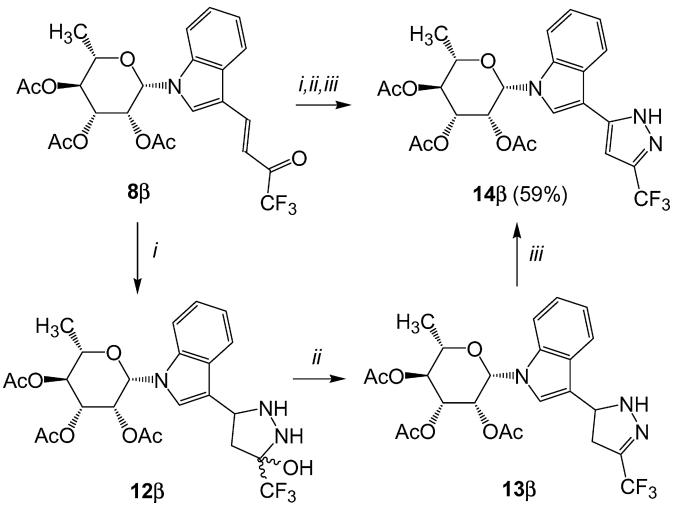
The cyclization of hydrazine hydrate with **8*α***, following the procedure described for the synthesis of **8*β***, afforded the *α*-configured 3-(pyrazol-3-yl)indol-*N*-rhamnoside **14*α*** in 62% yield (Sch. 5). Stirring of a methanol solution of **14*α*** in the presence of a catalytic amount of KO*t*Bu (0.06 equiv.) gave the deprotected rhamnoside **15*α*** in 77% yield.

The reaction of **8*α*** with 1,2-diaminoethane afforded the known[20–22] 3-formylindole-*N*-rhamnoside **16*α*** rather than the expected diazepine (Sch. 6). The formation of **16*α*** can be explained by conjugate addition of 1,2-diaminoethane to the enone and subsequent fragmentation by retro-aldol reaction. Likewise, the reaction of **8*α*** with other dinucleophiles, such as hydroxylamine or 1,2-diaminobenzene, proved to be unsuccessful.

The cytotoxic activity of products **8*β***, **14*α***, **14*β***, and **15*α*** against an immortalized human keratinocyte (HaCaT) cell line was studied (Table 2). The tests were carried out as previously reported.[23] A moderate activity was found for



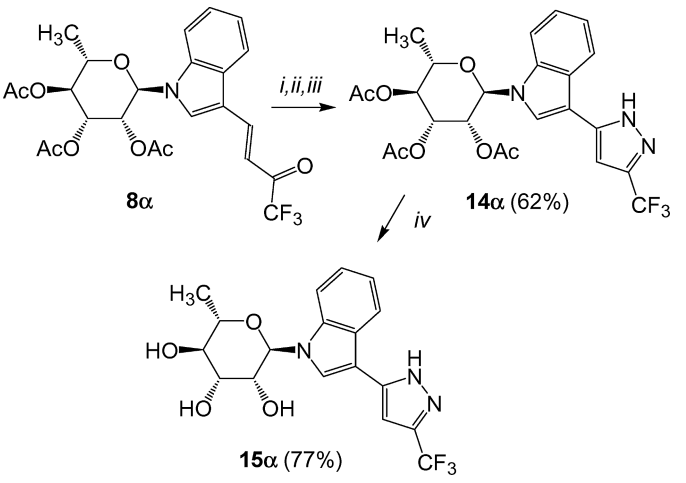
Scheme 3: (*α*-L-Rhamnopyranosyl)indole **8*α*** and (*β*-D-glucopyranosyl)indole **11*β***.



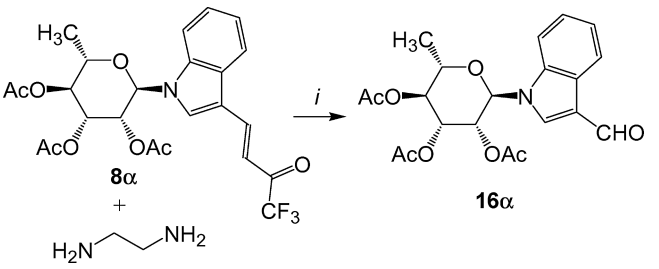
Scheme 4: Synthesis of 3-(pyrazol-3-yl)indol-*N*-rhamnoside **14*β***. *Reagents and conditions*: (*i*) $NH_2NH_2{\cdot}H_2O$, EtOH, 20°C, 20 min; (*ii*) *p*-toluenesulfonic acid, benzene, 90°C, 1 h; (*iii*) DDQ, dioxane, 20°C, 1 h.

14*α* and **14*β***. Interestingly, some activity was observed also for starting material **8*β***. The activity of deprotected glycoside **15*α*** was less than the activity of acetyl-protected derivative **14*α***.

In conclusion, the first 3-(3-pyrazolyl)indol-*N*-glycosides were prepared. They show a moderate cytotoxic activity against human keratinocytes (HaCaT).



Scheme 5: Synthesis of deprotected 3-(pyrazol-3-yl)indol-*N*-rhamnoside **15*α***. *Reagents and conditions*: (*i*) $NH_2NH_2{\cdot}H_2O$, EtOH, 20°C, 20 min; (*ii*) *p*-toluenesulfonic acid, benzene, 80°C, 1 h; (*iii*) DDQ, dioxane, 20°C, 1 h; (*iv*) KO*t*Bu, MeOH, 20°C, 12 h.



Scheme 6: Reaction of 8α with 1,2-diaminoethane. *Reagents and conditions:* (*i*) 1,2-diaminoethane, CH_3CN, 60°C, 20 h.

EXPERIMENTAL

General

^1H NMR spectra (250.13, 300.13, and 500.13 MHz) and ^{13}C NMR spectra (62.9, 75.5, and 125.8 MHz) were recorded on Bruker spectrometers AV II 250, AV III 300, and AV 500 in $CDCl_3$, DMSO-d_6, and C_6D_6 as solvents. The calibration of spectra was carried out on solvent signals [$CDCl_3$: d (^1H) 7.25, d (^{13}C) 77.0; DMSO-d_6: d (^1H) 2.50, d (^{13}C) 39.7; C_6D_6: d (^1H) = 7.16, d (^{13}C) 128.0]. Infrared spectra were recorded on a FTIR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane), or electrospray ionization (ESI). Melting points are uncorrected. Analytical thin layer chromatography was performed on 0.20-mm 60 A silica gel plates. Column chromatography was performed on 60 A silica gel (60–200 mesh).

Synthesis of Indole-*N*-rhamnosides 7α/β

To a stirred solution of indoline-*N*-glycoside **6** (**α/β** = 1:3, 2.00 g, 5.1 mmol) in dioxane was added DDQ (1.30 g, 5.6 mmol). The solution was stirred for 12 h at rt. An ice-cooled saturated aqueous solution of $NaHCO_3$ was added. The

Table 2: Results of the antiproliferative screening

Compound	IC_{50} (μmol/L)[a]
8β	34.5
14β	25.4
14α	21.1
15α	34.4

[a]Inhibition studies were performed in two separate experiments with six parallels each. Cell viability was detected using the Neutral Red Uptake assay (NRU).[24]

reaction mixture was filtered and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (heptanes/EtOAc = 8:1 → 4:1) to give **7** (**α/β** = 1:3, 1.75 g, 86%) as a colorless solid. The separation of the anomers was possible by repeated column chromatography (heptanes/EtOAc = 10:1 → 4:1). The fractions containing a mixture of the anomers were again separated together with collected fractions of anomeric mixtures from other syntheses in a second run and so on.

*1-(2′,3′,4′-Tri-*O*-acetyl-α-L-rhamnopyranosyl)indole (7α)*

m.p. = 147–149°C (heptane/EtOAc); $[\alpha]_D = -121.90$ ($c = 0.61$, $T = 23.1$°C, $CHCl_3$); $R_f = 0.20$ (heptane/EtOAc 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.62$ (d, $^3J = 7.4$ Hz, 1H, H-4/ H-7); 7.61 (d, $^3J = 8.1$ Hz, 1H, H-4/ H-7); 7.49 (d, $^3J_{2,3} = 3.4$ Hz, 1H, H-2); 7.23 ("t", $^3J = 7.8$ Hz, 1H, H-5/ H-6); 7.16 ("t", $^3J = 7.6$ Hz, 1H, H-5/ H-6); 6.61 (d, $^3J_{2,3} = 3.4$ Hz, 1H, H-3); 6.04 (t, $^3J_{1',2'} = {}^3J_{2',3'} = 3.0$ Hz, 1H, H-2′); 5.88 (d, $^3J_{1',2'} = 2.7$ Hz, 1H, H-1′); 5.46 (dd, $^3J_{2',3'} = 3.3$ Hz, $^3J_{3',4'} = 9.0$ Hz, 1H, H-3′); 5.23 (t, $^3J_{3',4'} = {}^3J_{4',5'} = 8.8$ Hz, 1H, H-4′); 3.57 (dq, $^3J_{5',6'} = 6.4$ Hz, $^3J_{4',5'} = 8.5$ Hz, 1H, H-5′); 2.15, 2.10, 2.04 (3s, 9H, 3 × C(O)CH_3); 1.26 (d, $^3J_{5',6'} = 6.4$ Hz, 3H, H-6′). ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 170.3$, 169.6, 169.5 (3 × *C*(O)CH_3); 136.5, 128.9 (C-3a, C-7a); 124.8, 122.4, 120.8, 120.6, 111.4, 103.9 (C-2, C-3, C-4, C-5, C-6, C-7); 81.5 (C-1′); 70.3, 70.0, 68.4, 67.7 (C-2′, C-3′, C-4′, C-5′); 20.5, 20.5, 20.4 (3 × C(O)*C*H_3); 16.8 (C-6′). MS (EI, 70eV): m/z (%) = 389 (63) [M^+], 273 (46) [M^+-aglycone], 153 (89) [M^+-aglycone-2HOAc], 117 (52) [indole]. HRMS (EI, 70eV): calcd. for $C_{20}H_{23}NO_7$ ([M^+]) 389.14690, found 389.14655.

*1-(2′,3′,4′-Tri-*O*-acetyl-β-L-rhamnopyranosyl)indole (7β)*

mp.. = 54–56°C (heptane/EtOAc); $[\alpha]_D = -24.20$ ($c = 0.68$, $T = 23.1$°C, $CHCl_3$); $R_f = 0.15$ (heptane/EtOAc 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.58$ (d, $^3J = 7.8$ Hz, 1H, H-4/ H-7); 7.40 (d, $^3J = 8.3$ Hz, 1H, H-4/ H-7); 7.24 (d, $^3J_{2,3} = 3.4$ Hz, 1H, H-2); 7.21 ("dt", $^4J = 1.2$ Hz, $^3J = 7.3$ Hz, $^3J = 8.3$ Hz, 1H, H-5/ H-6); 7.11 ("dt", $^4J = 1.1$ Hz, $^3J = 7.3$ Hz, 1H, H-5/ H-6); 6.51 (d, $^3J_{2,3} = 3.4$ Hz, 1H, H-3); 5.82 (d, $^3J_{1',2'} = 1.1$ Hz, 1H, H-1′); 5.55 (dd, $^3J_{1',2'} = 1.2$ Hz, $^3J_{2',3'} = 2.7$ Hz, 1H, H-2′); 5.31–5.18 (m, $^3J_{2',3'} = 2.8$ Hz, $^3J_{3',4'} = 10.2$ Hz, 2H, H-3′, H-4′); 3.86–3.73 (m, $^3J_{5',6'} = 6.2$ Hz, $^3J_{4',5'} = 9.2$ Hz, 1H, H-5′); 2.10, 2.01, 1.98 (3s, 9H, 3 × C(O)CH_3); 1.36 (d, $^3J_{5',6'} = 6.2$ Hz, 3H, H-6′). ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 170.1$, 169.9, 169.5 (3 × *C*(O)CH_3); 135.1, 128.6 (C-3a, C-7a); 125.1, 122.0, 121.0, 120.3, 109.7, 103.1 (C-2, C-3, C-4, C-5, C-6, C-7); 82.0 (C-1′); 73.7, 71.3, 70.1, 69.8 (C-2′, C-3′, C-4′, C-5′); 20.8, 20.7, 20.5 (3 × C(O)*C*H_3); 17.6 (C-6′). MS (EI, 70eV): m/z (%) = 389 (59) [M^+], 273 (26) [M^+-aglycone], 153 (75) [M^+-aglycone-2HOAc], 117 (40) [indole]. MS (EI, 70eV): calcd. for $C_{20}H_{23}NO_7$ ([M^+]) 389.14690, found 389.14646.

General Procedure for the Synthesis of *N*-glycosylated (*Trans*-1″,1″,1″-trifluoro-but-3″-en-2″-on-4″-yl)indoles

To a solution of the *N*-glycosylated indole in dichloromethane were added **3** (4.0 equiv.) and a catalytic amount of $ZnCl_2$. The reaction mixture was stirred at 20°C for 20 h and was subsequently filtered. The solvent was concentrated in vacuo and the residue was purified by column chromatography (heptane/EtOAc = 5:1 → 1:1).

*1-(2′,3′,4′-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-3-(*trans*-1″,1″,1″-trifluoro-but-3″-en-2″-one-4″-yl)indole (8β) and 1″,1″,1″-trifluoro-4″,4″-bis-[*N*-(2′,3′,4′-tri-*O*-acetyl-β-L-rhamno-pyranosyl)indol-3-yl]-butan-2″-one (9β)*

Starting with **7β** (1.10 g, 2.8 mmol) and **3** (1.90 g, 11.3 mmol), **8β** was isolated as a yellow solid (890 mg, 62%) and **9β** was isolated as a pale yellow solid (280 mg, 22%).

8β: m.p. = 183–184°C (heptane/EtOAc); $[\alpha]_D = +142.32$ ($c = 0.63$, $T = 21.7$°C, $CHCl_3$); $R_f = 0.49$ (heptane/EtOAc 1:3). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.16$ (d, $^3J_{3'',4''} = 15.6$ Hz, 1H, H-4″); 7.92–7.85 (m, 1H, Ar); 7.80 (s, 1H, H-2); 7.46–7.38 (m, 1H, Ar); 7.37–7.29 (m, 2H, Ar); 6.98 (d, $^3J_{3'',4''} = 15.6$ Hz, 1H, H-3″); 5.87 (d, $^3J_{1',2'} = 1.2$ Hz, 1H, H-1′); 5.58 (dd, $^3J_{1',2'} = 1.2$ Hz, $^3J_{2',3'} = 2.6$ Hz, 1H, H-2′); 5.33–5.19 (m, $^3J_{2',3'} = 2.6$ Hz, $^3J_{3',4'} = 10.1$ Hz, 2H, H-3′, H-4′); 3.91–3.79 (m, $^3J_{5',6'} = 6.2$ Hz, 1H, H-5′); 2.11, 1.99, 1.99 (3s, 9H, 3 × C(O)CH_3); 1.40 (d, $^3J_{5',6'} = 6.2$ Hz, 1H, H-6′). ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 179.9$ (q, $^2J_{C,F} = 34.5$ Hz, *C*(O)CF_3); 170.1, 169.8, 169.3 (3 × *C*(O)CH_3); 143.3 (C-4″); 136.3 (C_{qu}); 133.5 (C-2); 125.5 (C_{qu}); 124.1, 123.1, 121.0 (3 × CH_{Ar}); 116.8 (q, $^1J_{C,F} = 291.6$ Hz, CF_3); 114.0 (C_{qu}); 112.1 (C-3″); 110.5 (CH_{Ar}); 82.0 (C-1′); 74.2 (C-5′); 70.9, 69.7 (C-3′, C-4′); 68.9 (C-2′); 20.7, 20.5, 20.5 (3 × C(O)*C*H_3); 17.6 (C-6′). ^{19}F NMR (235 MHz, $CDCl_3$): −77.20 (CF_3). MS (EI, 70 eV): m/z (%) = 511 (66) [M^+], 273 (28) [M^+-aglycone], 239 (11) [aglyconeH], 153 (100) [M^+-aglycone-2HOAc]. HRMS (EI, 70eV): calcd. for $C_{24}H_{24}F_3NO_8$ ([M^+]) 511.14485, found 511.14471. Anal. calcd. for $C_{24}H_{24}F_3NO_8$ (511.44): C, 56.36; H, 4.73; N, 2.74. Found: C, 56.22; H, 4.69; N, 2.68.

9β: m.p. = 149–150°C (heptane/EtOAc); $R_f = 0.38$ (heptane/EtOAc = 1:3). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.55$ (d, $^3J = 7.9$ Hz, 1H, Ar); 7.34 (m, $^3J = 7.6$ Hz, $^3J = 7.9$ Hz, 3H, Ar); 7.23–7.08 (m, 3H, Ar); 7.12, 6.96 (2s, 2H, 2 × H-2); 7.00 ("t", $^3J = 7.6$ Hz, 1H, Ar); 5.77, 5.72 (2d, $^3J_{1',2'} = 1.2$ Hz, 2H, 2 × H-1′); 5.58, 5.42 (2dd, $^3J_{1',2'} = 1.2$ Hz, $^3J_{2',3'} = 2.6$ Hz, 2H, 2 × H-2′); 5.25–5.09 (m, 5H, 2 × H-3′, 2 × H-4′, H-4″); 3.86–3.69 (m, $^3J_{5',6'} = 6.1$ Hz, $^3J_{4',5'} = 9.1$ Hz, 2H, 2 × H-5′); 3.52 (d, $^3J_{3'',4''} = 7.1$ Hz, 2H, CH_2); 2.10, 2.07, 1.98, 1.93, 1.91, 1.45 (6s, 18H, 5 × C(O)CH_3); 1.39, 1.32 (2d, $^3J_{5',6'} = 6.2$ Hz, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 189.6$ (q, $^2J_{C,F} = 35.3$ Hz, *C*(O)CF_3); 170.1, 170.1, 169.8, 169.8, 169.5, 169.4 (6 × *C*(O)CH_3); 135.8, 135.7, 127.2, 126.7 (4 × C_{qu}); 123.5, 122.6, 122.4, 122.1, 120.4, 120.3, 119.7, 119.0 (8 × CH_{Ar}); 118.1, 117.5

($2 \times C_{qu}$); 115.5 (q, $^1J_{C,F} = 293.0$ Hz, CF_3); 109.9, 109.9 ($2 \times CH_{Ar}$); 82.2, 81.7 (2xC-1′); 73.8, 73.7 ($2 \times$ C-5′); 71.4, 71.3, 70.1, 70.0 (C-3′, C-4′); 69.6, 69.6 (C-2′); 42.5 (C-3″); 28.1 (C-4″); 20.8, 20.7, 20.6, 20.5, 20.4, 19.8 ($6 \times C(O)CH_3$); 17.6, 17.5 ($2 \times$ C-6′). ^{19}F NMR (235 MHz, $CDCl_3$): −79.07 (CF_3). MS (EI, 70 eV): m/z (%) = 900 (34) [M^+], 789 (100) [M^+-$CH_2C(O)CF_3$], 517 (20) [M^+-$CH_2C(O)CF_3$-sugarH], 111 (84) [$CH_2C(O)CF_3$]. Anal. calcd. for $C_{44}H_{47}F_3N_2O_{15}$ (900.29): C, 58.66; H, 5.26; N, 3.11. Found: C, 58.47; H, 5.27; N, 2.86.

*1-(2′,3′,4′-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-3-(*trans-*1″,1″,1″-trifluoro-but-3″-en-2″-on-4″-yl)indole (**8α**)*

Starting with **7α** (1.00 g, 2.6 mmol), **8α** was isolated as a yellow solid (930 mg, 71%). m.p. = 114–116°C (heptane/EtOAc); $[\alpha]_D = -94.55$ ($c = 1.01$, $T = 21.5$°C, $CHCl_3$); $R_f = 0.45$ (heptane/EtOAc 1:3). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (d, $^3J_{3'',4''} = 15.8$ Hz, 1H, H-4″); 7.98 (s, 1H, H-2); 7.95–7.88 (m, $^3J = 7.5$ Hz, 1H, Ar); 7.70–7.63 (m, $^3J = 7.5$ Hz, 1H, Ar); 7.41–7.33 (m, $^3J = 7.2$ Hz, 2H, Ar); 7.04 (d, $^3J_{3'',4''} = 15.8$ Hz, 1H, H-3″); 5.97 (t, $^3J_{1',2'} = {}^3J_{2',3'} = 3.3$ Hz, 1H, H-2′); 5.94 (d, $^3J_{1',2'} = 3.5$ Hz, 1H, H-1′); 5.35 (dd, $^3J_{2',3'} = 3.1$ Hz, $^3J_{3',4'} = 8.5$ Hz, 1H, H-3′); 5.20 (t, $^3J_{3',4'} = {}^3J_{4',5'} = 8.5$ Hz, 1H, H-4′); 3.63 (quintet, $^3J_{5',6'} = 6.2$ Hz, 1H, H-5′); 2.13, 2.12, 2.07 (3s, 9H, $3 \times C(O)CH_3$); 1.30 (d, $^3J_{5',6'} = 6.2$ Hz, 3H, H-6′). ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 179.9$ (q, $^2J_{C,F} = 34.8$ Hz, $C(O)CF_3$); 170.5, 170.5, 169.6 ($3 \times C(O)CH_3$); 143.0 (C-4″); 138.0 (C_{qu}); 132.6 (C-2); 126.1 (C_{qu}); 124.6, 123.3, 120.8 (3s, $3 \times CH_{Ar}$); 116.8 (q, $^1J_{C,F} = 290.5$ Hz, CF_3); 114.7 (C_{qu}); 112.9 (C-3″); 112.5 (CH_{Ar}); 81.2 (C-1′); 70.0 (C-5′); 70.0, 69.8 (C-3′, C-4′); 67.3 (C-2′); 20.7, 20.6, 20.6 ($3 \times C(O)CH_3$); 16.8 (C-6′). ^{19}F NMR (235 MHz, $CDCl_3$): −77.27 (CF_3). MS (EI, 70eV): m/z (%) = 511 (38) [M^+], 273 (77) [M^+-aglycone], 239 (12) [aglyconeH], 153 (89) [M^+-aglycone-2HOAc], 111 (95) [$CH_2C(O)CF_3$]. HRMS (EI, 70eV): calcd. for $C_{24}H_{24}F_3NO_8$ ([M^+]) 511.14485, found 511.14453.

*1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(*trans-*1″,1″,1″-trifluoro-but-3″-en-2″-on-4″-yl)indole (**11β**)*

Starting with indolglycoside **10β** (500 mg, 1.12 mmol), 1-(2′,3′,4′,6′-tetra-*O*-acetyl-α-L-glucopyranosyl)-3-(*trans*-1″,1″,1″-trifluoro-but-3″-en-2″-one-4″-yl)indole **11β** resulted as a yellow solid (300 mg, 47%). m.p. 208–210°C (heptane/EtOAc); $[\alpha]_D$ −85.11 (c 1.02, T 21.7°C, $CHCl_3$); R_f 0.35 (heptane/EtOAc = 1:3). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.16$ (d, $^3J_{3'',4''} = 15.8$ Hz, 1H, H-4″); 7.93–7.86 (m, 1H, Ar); 7.73 (s, 1H, H-2); 7.51–7.45 (m, 1H, Ar); 7.42–7.31 (m, 2H, Ar); 7.00 (d, $^3J_{3'',4''} = 15.8$ Hz, 1H, H-3″); 5.64 (d, $^3J_{1',2'} = 8.9$ Hz, 1H, H-1′); 5.52–5.43 (m, $^3J = 9.2$ Hz, 2H, H-2′, H-3′); 5.29 (t, $^3J_{3',4'} = {}^3J_{4'',5''} = 9.8$ Hz, 1H, H-4′); 4.33 (dd, $^3J_{5',6a'} = 5.0$ Hz, $^2J_{6a',6b'} = 12.7$ Hz, 1H, H-6a′); 4.17 (dd, $^3J_{5',6b'} = 2.1$ Hz, $^2J_{6a',6b'} = 12.7$ Hz, 1H, H-6b′); 4.03 (ddd, $^3J_{5',6b'} = 2.1$ Hz, $^3J_{5',6a'} = 5.0$ Hz, 1H, H-5′); 2.09, 2.08, 2.02, 1.67 (4s, 12H, $4 \times C(O)CH_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.9 (q, $^2J_{C,F}$ = 34.4 Hz, *C*(O)CF_3); 170.5, 170.0, 169.3, 168.6 (4 × *C*(O)CH_3); 142.9 (C-4″); 137.4 (C_{qu}); 132.2 (C-2); 126.1 (C_{qu}); 124.4, 123.2, 121.1 (3 × CH); 116.6 (q, $^1J_{C,F}$ = 291.0 Hz, CF_3); 114.9 (C_{qu}); 113.0 (C-3″); 110.7 (CH); 82.3 (C-1′); 75.1 (C-5′); 72.8, 70.6 (C-2′, C-3′); 67.8 (C-4′); 61.6 (C-6′); 20.7, 20.5, 20.5, 20.0 (4 × C(O)*C*H_3). ^{19}F NMR (235 MHz, $CDCl_3$): −77.35 (CF_3). MS (EI, 70eV): m/z (%) = 569 (28) [M^+], 331 (30) [M^+-aglycone], 169 (100) [M^+-aglycone-2HOAc], 109 (90). HRMS (EI, 70eV): calcd. for $C_{26}H_{26}F_3NO_{10}$ ([M^+]) 569.15033, found 569.15033.

General Procedure for the Synthesis of *N*-glycosidated (5′-Trifluoromethyl-*2′H*-pyrazol-3′-yl)indoles

To an EtOH solution of **8** was added hydrazine hydrate (1.2 equiv.) and the mixture was stirred at 20°C for ca. 20 min (TLC control). The solvent was removed in vacuo. To the residue was added dry benzene and a catalytic amount of *o,p*-toluenesulfonic acid and the mixture was stirred at 90°C for 1 h until the reaction was complete (TLC-control). The solution was allowed to cool to 20°C and NEt_3 was added. The solvent was concentrated in vacuo and the residue was dissolved in dry dioxane. To the solution was added DDQ (1.1 equiv.) and the solution was stirred at 20°C for 1 h until the reaction was complete (TLC-control). An ice-cooled saturated aqueous solution of $NaHCO_3$ was added. The reaction mixture was filtered and the aqueous solution was extracted with EtOAc (three times). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (heptane/EtOAc = 4:1 → 2:1).

*1-(2″,3″,4″-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-3-(5′-trifluoromethyl-2′*H*-pyrazol-3′-yl)indole (**14β**)*

Starting with **8β** (300 mg, 0.6 mmol), **14β** was isolated as a slightly yellow solid (180 mg, 59%). Intermediates **12β** (R_f = 0.19 (heptane/EtOAc)) and **13β** (R_f = 0.62 (heptane/ EtOAc)) were used crude. m.p. = 122–124°C (heptane/EtOAc); $[\alpha]_D$ = +47.20 (c = 1.06, T = 22.0°C, $CHCl_3$); R_f = 0.46 (heptane/EtOAc = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74, 7.49 (2″dd″, ^4J = 1.5 Hz, ^3J = 7.3 Hz, 2H, H-4, H-7); 7.60 (s, 1H, H-2); 7.33–7.19 (m, ^4J = 1.4 Hz, ^3J = 7.3 Hz, 2H, H-5, H-6); 6.76 (s, 1H, H-4′); 5.91 (d, $^3J_{1″,2″}$ = 1.1 Hz, 1H, H-1″); 5.61 (dd, $^3J_{1″,2″}$ = 1.2 Hz, $^3J_{2″,3″}$ = 2.9 Hz, 1H, H-2″); 5.35–5.21 (m, $^3J_{2″,3″}$ = 2.9 Hz, $^3J_{3″,4″}$ = 10.2 Hz, $^3J_{4″,5″}$ = 9.3 Hz, 2H, H-3″, H-4″); 3.85 (m, $^3J_{4″,5″}$ = 9.2 Hz, $^3J_{5″,6″}$ = 6.2 Hz, 1H, H-5″); 2.11, 1.99, 1.96 (3s, 9H, 3 × C(O)CH_3); 1.39 (d, $^3J_{5″,6″}$ = 6.2 Hz, 3H, H-6″). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 169.9, 169.9 (3 × *C*(O)CH_3); 143.7 (q, $^2J_{C,F}$ = 38.1 Hz, C-5′); 139.2, 135.4, 125.5 (3 × C_{qu}); 121.3 (q, $^1J_{C,F}$ = 268.4 Hz, CF_3); 123.7 (C-2); 123.5, 121.8 (C-5, C-6); 119.5, 110.8 (C-4, C-7); 105.6 (C_{qu}); 101.1 (q, $^3J_{C,F}$ = 2.0 Hz, C-4′); 82.5 (C-1″); 74.0 (C-5″); 71.3, 69.9 (C-3″, C-4″); 69.7 (C-2″); 20.8, 20.7, 20.6 (3 × C(O)*C*H_3); 17.6

(C-6″). ^{19}F NMR (282 MHz, $CDCl_3$): −62.07 (CF_3). MS (EI, 70eV): *m/z* (%) = 523 (37) [M^+], 273 (18) [M^+-aglycone], 251 (29) [aglyconeH], 153 (91) [M^+-aglycone-2HOAc]. HRMS (EI, 70eV): calcd for $C_{24}H_{24}F_3N_3O_7$ ([M^+]) 523.15609, found 523.15458. Anal. calcd. for (523.46): C, 55.07; H, 4.62; N, 8.03. Found: C, 55.06; H, 4.59; N, 8.16.

*1-(2″,3″,4″-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-3-(5′-trifluoromethyl-*2′H*-pyrazol-3′-yl)indole (**14α**)*

Starting with **8α** (300 mg, 0.6 mmol), **14α** was isolated as a slightly yellow solid (190 mg, 62%). Intermediates **12α** (R_f = 0.17 (heptane/EtOAc)) and **13α** (R_f = 0.59 (heptane/ EtOAc)) were used in crude form. m.p. = 76–79°C (heptane/EtOAc); $[\alpha]_D$ −101.31 (c = 0.60, T = 22.8°C, $CHCl_3$); R_f = 0.43 (heptane/EtOAc = 1:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.85–7.79 (m, 1H, Ar); 7.82 (s, 1H, H-2); 7.68 ("dd", ^4J = 1.7 Hz, ^3J = 7.3 Hz, 1H, Ar); 7.38–7.27 (m, ^4J = 1.6 Hz, ^3J = 7.3 Hz, 2H, Ar); 6.83 (s, 1H, H-4′); 6.04 (t, $^3J_{1'',2''} = {}^3J_{2'',3''}$ = 3.1 Hz, 1H, H-2″); 5.95 (d, $^3J_{1'',2''}$ = 2.9 Hz, 1H, H-1″); 5.41 (dd, $^3J_{2'',3''}$ = 3.2 Hz, $^3J_{3'',4''}$ = 9.0 Hz, 1H, H-3″); 5.22 (t, $^3J_{3'',4''} = {}^3J_{4'',5''}$ = 8.6 Hz, 1H, H-4″); 3.62 (m, $^3J_{4'',5''}$ = 8.0 Hz, $^3J_{5'',6''}$ = 6.4 Hz, 1H, H-5″); 2.15, 2.08, 2.05 (3s, 3 × C(O)CH_3); 1.29 (d, $^3J_{5'',6''}$ = 6.4 Hz, 1H, H-6″). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 169.9, 169.8 (3 × *C*(O)CH_3); 143.5 (q, $^2J_{C,F}$ = 37.9 Hz, C-5′); 138.8, 137.0, 125.8 (3 × C_{qu}); 123.8 (C-2); 123.1, 122.1 (2 × CH); 121.4 (q, $^1J_{C,F}$ = 268.8 Hz, CF_3); 119.5, 112.2 (2 × CH); 106.7 (C_{qu}); 101.1 (q, $^3J_{C,F}$ = 2.0 Hz, C-4′); 81.5, 70.2, 70.1, 69.3, 67.6 (C-1″, C-2″, C-3″, C-4″, C-5″); 20.7, 20.6, 20.5 (3 × C(O)*C*H_3); 16.9 (C-6″). ^{19}F NMR (235 MHz, $CDCl_3$): δ = 62.08 (CF_3). MS (EI, 70 eV): *m/z* (%) = 523 (34) [M^+], 273 (63) [M^+-aglycone], 251 (44) [aglyconeH], 153 (93) [M^+-aglycone-2HOAc]. HRMS (EI, 70 eV): calcd. for $C_{24}H_{24}F_3N_3O_7$ ([M^+]) 523.15609, found 523.15526.

*1-α-L-Rhamnopyranosyl-3-(5′-trifluoromethyl-*2′H*-pyrazol-3′-yl)indole (**15α**)*

To a methanol solution of **14α** (150 mg, 0.3 mmol) was added KO*t*Bu (0.02 equiv. per acetyl group). The mixture was stirred for 10 to 12 h at 20°C, subsequently neutralized by addition of ion exchange resin IR 120 (H^+), and filtered. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography ($CHCl_3$/EtOH = 20:1 → 5:1) to give the desired glycoside **15α** as a pale yellow solid (88 mg, 77%). m.p. = 116–117°C; $[\alpha]_D$ = −54.66 (c = 1.10, T = 21.6°C, CH_3OH); R_f = 0.35 ($CHCl_3$/ EtOH = 5:1). ^{1}H NMR (300 MHz, CD_3OD): δ = 7.85 (s, 1H, H-2); 7.82, 7.70 (2"dd", ^4J = 1.5 Hz, ^3J = 7.4 Hz, 2H, H-4, H-7); 7.26 (m, ^4J = 1.5 Hz, ^3J = 7.4 Hz, 2H, H-5, H-6); 6.89 (s, 1H, H-4′); 5.98 (d, $^3J_{1'',2''}$ = 4.8 Hz, 1H, H-1″); 4.56 (dd, $^3J_{2'',3''}$ = 3.5 Hz, $^3J_{1'',2''}$ = 4.7 Hz, 1H, H-2″); 4.08 (dd, $^3J_{2'',3''}$ = 3.5 Hz, $^3J_{3'',4''}$ = 6.7 Hz, 1H, H-3″); 3.69 (t, $^3J_{3'',4''} = {}^3J_{4'',5''}$ = 6.6 Hz, 1H, H-4″); 3.54 (quintett, $^3J_{4'',5''} = {}^3J_{5'',6''}$ = 6.6 Hz, 1H, H-5″); 1.38 (d, $^3J_{5'',6''}$ = 6.6 Hz, 1H, H-6″). ^{13}C NMR (75 MHz, CD_3OD):

$\delta = 144.4$ (q, $^2J_{C,F} = 37.7$ Hz, C-5′); 140.8, 138.7, 127.1 (3 × C_{qu}); 125.3 (C-2); 124.1, 122.5 (C-5, C-6); 123.1 (q, $^1J_{C,F} = 268.2$ Hz, CF_3); 120.3, 113.0 (C-4, C-7); 106.5 (C_{qu}); 101.3 (C-4′); 83.6 (C-1″); 74.0 (C-4″); 73.9 (C-5″); 73.6 (C-3″); 69.6 (C-2″); 17.5 (C-6″). ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = 63.45$ (CF_3). MS (EI, 70 eV): m/z (%) = 397 (23) [M^+], 251 (100) [aglyconeH]. HRMS (EI, 70 eV): calcd. for $C_{18}H_{18}F_3N_3O_4$ ([M^+]) 397.12439, found 397.12468.

Biological Studies (NRU Assay)

The screening toward cytotoxic properties was performed in accordance to the NIH protocols. The cell viability was investigated using the Neutral Red Uptake assay.[22] Briefly, HaCaT keratinocytes were seeded into wells of a 96-well plate using RPMI medium with fetal calf serum. After the recovery phase, diluted compounds in fresh RPMI were added and cells left undisturbed for 72 h. At the end of incubation, cells were incubated with RPMI containing neutral red. Following washing and dissolving of deposited neutral red, OD was measured at 550 nm. Stock solutions of the test compounds were prepared using DMSO. Etoposide was used as the positive control experiment and DMSO as the negative control experiment. Experimental data were acquired by two independent experiments with six parallel dilutions.

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