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# Glycosidopyrroles
# Part 3. Effect of the benzocondensation on acyclic derivatives: 1-(2-hydroxyethoxy)methylindoles as potential antiviral agents [1]

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**Abstract**

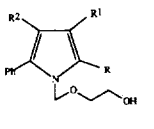
The new of 1-(2-hydroxyethoxy)methylindole derivatives **3a–i** were prepared in good yields. None of them showed any significant anti-HIV activity and therefore the benzocondensation between the 2 and 3 positions of the pyrrole ring definitely reduced the weak activity found in the analogues **1a–c**. 

*Keywords:* Antiviral agents; Acyclic glycosidoindoles; 1-(2-Hydroxyethoxy)methylindoles

## 1. Introduction

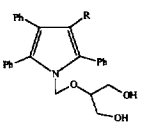
In connection with our research project on nucleoside analogues incorporating the pyrrole moiety, we recently reported the synthesis and biological evaluation of some acyclic glycosidopyrroles of type **1** and **2** that could behave as selective inhibitors of herpes virus, being closely related to acyclovir and ganciclovir, at least as far as the acyclic moiety is concerned [1,2].

All the tested 1-hydroxyethoxymethylpyrroles were generally inactive against both HIV-1 and HSV types 1 and 2, but showed considerable cytotoxicity. Only the nitro-triphenyl derivative **1a** was found to inhibit the HIV-1 replication at concentrations that were not cytotoxic for MT-4 cells, and inhibited the HSV-2 strain at concentrations slightly below those cytotoxic for Vero cells. Also, derivatives **1b** and **1c** showed weak anti-HSV activity. However, a linear relationship between the observed cytotoxicity and the lipophilicity was found for this series of compounds: derivatives with high lipophilicity were also highly cytotoxic.



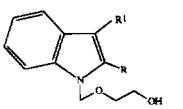
1 a–c

a R=R¹=Ph, R²=NO₂
b R=Me, R¹=COOEt, R²=Cl
c R=Ph, R¹=COOEt, R²=NO₂



2 a–c

a R=Br S.I.=1.5
b R=NH₂ S.I.=9.3
c R=N₃ S.I.=2



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In the case of the pyrroles of type **2**, in which the acyclic chain of ganciclovir was incorporated, again the more interesting compounds, derivatives **2a–c**, belonged to the triphenyl substituted series. A modest selectivity against human immunodeficiency virus (HIV), as shown by the SI values, was found. The most active compound of the series was the 3-amino derivative. The lipophilicity may play a role since all the active derivatives have log *P* values in the range 4.49–6.06. Moreover, the only derivative of the 1-(2-hydroxyethoxy)methyl series with anti-HIV activity, **1a**, had similar lipophilicity (log $P = 5.60$).

In this paper we report the synthesis and biological evaluation of indole derivatives of type **3** to explore the effect of

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[1] A preliminary account of this work was presented at XIII Convegno Nazionale della Divisione di Chimica Farmaceutica della Società Chimica Italiana, Paestum, Italy, September 1996, abstr. p. 163.

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the benzocondensation between positions 2 and 3 of the pyrrole ring.

## 2. Chemistry

The synthesis of 1-(2-hydroxyethoxy)methylindoles of type **3** was achieved according to Scheme 1. The 1H-indoles **4a–g**, suitably substituted at position 3 with an electron-withdrawing group, were reacted with sodium hydride in acetonitrile to give the corresponding sodium salts. The latter compounds were condensed with (2-acetoxyethoxy)methyl bromide **5**, which was prepared from dioxolane and acetyl bromide [3]. 1-(2-Acetoxyethoxy)methyl derivatives of type **6** were isolated in excellent yields following reactions carried out over 2 hours at room temperature.

Removal of the protecting group with sodium methoxide in methanol, at room temperature for 30 min, gave derivatives **3a–g** in quantitative yields.

Compounds **3e,g**, bearing a nitro group in $R^1$, were catalytically reduced to give the corresponding 3-amino derivatives **3h,i** in good yields.

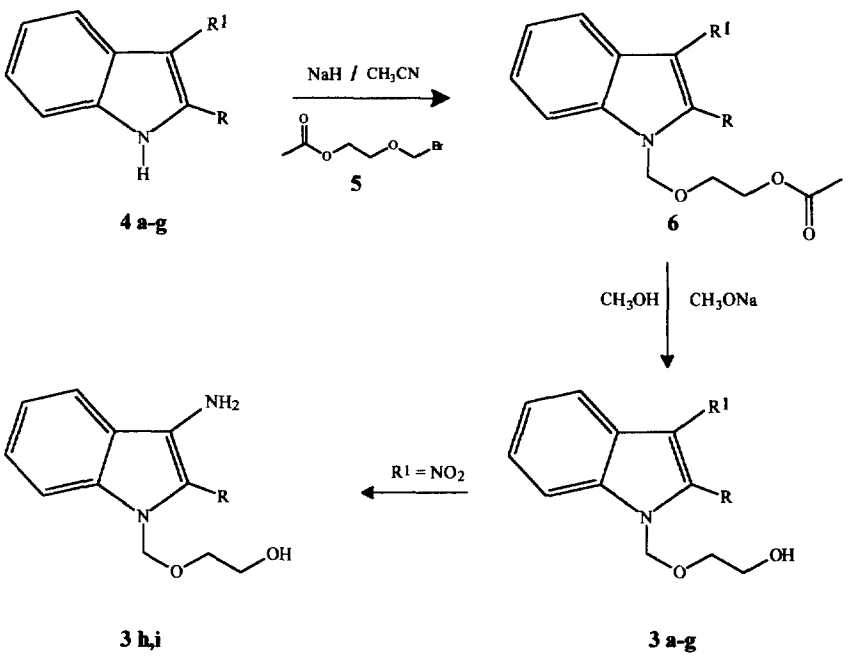
## 3. Biological results and conclusions

The cytotoxicity of glycosidoindole derivatives was evaluated in vitro in $CD4^+$ lymphocytes (MT-4). Compounds were also evaluated for antiviral activity against HIV in MT-4.

The antibacterial activity was tested against Gram-positive (*Staphylococcus aureus*, group D *Streptococcus*), and Gram-negative (*Salmonella* sp., *Shigella* sp.) bacteria, whereas the antimycotic activity was evaluated against *Candida albicans*, and *C. paratropicalis*, *Aspergillus fumigatus* and *Criptococcus neoformans*.

The cytotoxicity of test compounds, evaluated by measuring the number of viable cells, was found to range between 50 and 200 μM. The data are shown in Table 1 together with the parameter chosen to define the lipophilicity of title compounds: i.e. the log *P* values calculated with the Oxford Molecular software TSAR V2.41 using the atomic log *P* values determined according to Ref. [4].

The highest cytotoxicity correlates with the presence of the phenyl ring at position 2, no matter what the substituent $R^1$ is, the most cytotoxic compound being 3-amino-2-(2-pyridinyl)indole **3i**.




| | R | $R^1$ |
|---|---|---|
| a | H | CN |
| b | H | COMe |
| c | H | CHO |
| d | Ph | Br |
| e | Ph | $NO_2$ |
| f | 2-Pyridinyl | Br |
| g | 2-Pyridinyl | $NO_2$ |
| h | Ph | |
| i | 2-Pyridinyl | |

Scheme 1. Synthesis of 1-(2-hydroxyethoxy)methylindoles **3a–i**.

Table 1
Cytotoxicity, antiviral activity [a] and lipophilicity index of indole derivatives

| Comp. | $CC_{50}$ [b] | $EC_{50}$ [c] | log *P* |
|---|---|---|---|
| **6a** | >200 | >200 | 2.142 |
| **6b** | >200 | >200 | 1.263 |
| **6c** | >200 | >200 | 1.630 |
| **6d** | 120 | >120 | 4.195 |
| **6e** | >200 | >200 | 3.357 |
| **6f** | ≥200 | >200 | 3.747 |
| **6g** | >200 | >200 | 2.909 |
| **3a** | >200 | >200 | 2.013 |
| **3b** | >200 | >200 | 1.134 |
| **3c** | ≥200 | >200 | 1.501 |
| **3d** | 117 | >117 | 3.928 |
| **3e** | 154 | >154 | 3.228 |
| **3f** | >200 | >200 | 3.016 |
| **3g** | >200 | >200 | 2.780 |
| **3h** | 105 | >105 | 2.491 |
| **3i** | 50 | >50 | 2.043 |
| AZT | 150 | 0.01 | |

[a] Data represent mean values for three separate experiments. Variation among duplicate samples was less than 15%.
[b] Compound concentration (μM) required to reduce the multiplication of MT-4 cells by 50%.
[c] Compound concentration (μM) required to reduce the virus-induced cytopathogenicity (HIV-1) by 50%.

When evaluated for their ability to prevent the virus-induced cytopathogenicity in cell cultures infected at low multiplicity of infection, none of the tested compounds was found to inhibit the HIV-1 multiplication. These results are not unexpected if lipophilicity plays a role in modulating cytotoxicity and antiviral activity: derivatives of the indole series had log *P* values in the range 2.04–3.93, lower than those found in pyrrole analogues.

In conclusion the benzocondensation between positions 2 and 3 of the pyrrole ring definitely reduced the weak activity found in the corresponding pyrrole derivatives.

None of the compounds showed antibacterial or antifungal activity.

## 4. Experimental

### *4.1. Chemistry*

All melting points were taken on a Büchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Jasco FT-IR 5300 spectrophotometer; $^1H$ and $^{13}C$ NMR spectra were measured at 200 and 50.3 MHz using a Bruker AC-E series 200 MHz spectrometer (tetramethylsilane (TMS) as internal reference). Column chromatography was performed with Merck silica gel 230–400 mesh (ASTM). Elemental analyses for all new compounds were within ±0.4% of theoretical values. Chemical and spectral data of new compounds are reported in Table 2.

1*H*-Indole derivatives **4a–c** and 2-phenylindole were purchased from Aldrich. 2-(2-Pyridinyl)indole was prepared according to the procedure reported in Ref. [5]. 3-Bromoindoles **4d,f** were prepared by bromination of 2-phenyl- and 2-(2-pyridinyl)indoles respectively, with *N*-bromosuccinimide (NBS) in *N,N*-dimethylformamide (DMF) at room temperature according to the known procedure [6]: 3-bromo-2-phenylindole **4d**, yield 90%, m.p. 48–50°C (Ref. [7], m.p. 78–79°C); 3-bromo-2-(2-pyridinyl)indole **4f**, yield 92%, m.p. 111–112°C.

2-Phenyl- and 2-(2-pyridinyl)indoles were nitrated with amyl nitrite in benzene at reflux according to the procedure reported in Ref. [8]: 3-nitro-2-phenylindole **4e**, yield 79%, m.p. 239–241°C (Ref. [9], m.p. 236–238°C); 3-nitro-2-(2-pyridinyl)indole **4g**, yield 62%, m.p. 182–184°C (Ref. [8], m.p. 204–205°C).

(2-Acetoxyethoxy)methyl bromide **5** was prepared from 1,3-dioxolane and acetyl bromide according to Ref. [3].

### *4.2. General method for the preparation of 1-(2-acetoxyethoxy)methylindoles **6a–g***

Sodium hydride (6 mmol, 55% oil dispersion) was added at room temperature to a solution of indoles **4a–g** (5 mmol) in acetonitrile (30 ml). A solution of **5** (10 mmol) in acetonitrile (20 ml), stirred for 30 min, was added dropwise and the reactants were stirred at room temperature until disappearance of the starting material (thin-layer chromatographic (TLC) monitoring, 2 h). The solvent was evaporated under reduced pressure, and the crude residue was purified by column chromatography to give compounds **6a–g**.

### *4.3. General method for the preparation of 1-(2-hydroxyethoxy)methylindoles **3a–g***

A solution of sodium methoxide (5 mmol) in methanol (10 ml) was added dropwise to a solution of compounds **6a–g** (5 mmol) in methanol (30 ml). The reactants were stirred at room temperature until disappearance of the starting materials (TLC monitoring, 30 min). The solvent was evaporated under reduced pressure and the residue was washed with water, extracted with dichloromethane, and dried over sodium sulfate. Removal of the solvent in vacuo gave a crude residue which was purified by column chromatography to give compounds **3a–g**.

### *4.4. Preparation of 3-amino-1-(2-hydroxyethoxy)-methylindoles **3h, i***

A solution of nitro derivatives **3e,g** (5 mmol) in ethanol was reduced overnight over 10% Pd on charcoal in a Parr apparatus at 50 psi at room temperature. Removal of the catalyst and evaporation of the solvent under reduced pressure gave the amino derivatives which were recrystallized.

### *4.5. Biological assays*

All the experiments were carried out according to the procedures already described [1].

Table 2
Chemical and spectroscopic data of new compounds

| Comp. | Yield (%) | M.p. (°C) [a] | IR ($cm^{-1}$) | NMR [$(CD_3)_2SO$] [b] δ (ppm) | |
|---|---|---|---|---|---|
| | | | | $^1H$ | $^{13}C$ |
| **6a** | 60 | 65 (A) | 2220 (CN), 1734 (CO) | 1.89 (1H, s, $CH_3$), 3.62 (2H, t, $J$=4.4 Hz, $CH_2$), 4.06 (2H, t, $J$=4.4 Hz, $CH_2$), 5.71 (2H, s, $CH_2$), 7.32 (1H, dt, $J$=7.3, 1.5 Hz, H-5), 7.39 (2H, dt, $J$=7.3, 1.5 Hz, H-6), 7.68 (1H, dd, $J$=7.3, 1.5 Hz, H-7), 7.76 (1H, dd, $J$=7.3, 1.5 Hz, H-4), 8.44 (1H, s, H-2) | 20.42 (q), 62.61 (t), 66.17 (t), 75.94 (t), 84.93 (s), 112.04 (d), 115.56 (s), 118.79 (d), 122.56 (d), 123.94 (d), 127.25 (s), 135.17 (s), 137.36 (d), 170.54 (s) |
| **6b** [b] | 72 | 77 (B) | 1738 (CO), 1649 (CO) | 1.93 (3H, s, $CH_3$), 2.47 (3H, s, $CH_3$), 3.60 (2H, t, $J$=4.4 Hz, $CH_2$), 4.11 (2H, t, $J$=4.4 Hz, $CH_2$), 5.50 (2H, s, $CH_2$), 7.27 (1H, dt, $J$=6.4, 1.0 Hz, H-5), 7.30 (1H, dt, $J$=6.4, 1.0 Hz, H-6), 7.46 (1H, dd, $J$=6.4, 1.0 Hz, H-7), 7.77 (1H, s, H-2), 8.36 (1H, dd, $J$=6.4, 1.0 Hz, H-4) | 20.82 (q), 27.54 (q), 62.79 (t), 66.47 (t), 76.77 (t), 110.46 (d), 117.97 (s), 122.59 (d), 123.06 (d), 123.85 (d), 126.60 (s), 134.77 (d), 136.80 (s), 170.67 (s), 193.19 (s) |
| **6c** | 91 | 57–59 (A) | 1736 (CO), 1660 (CO) | 1.89 (3H, s, $CH_3$), 3.63 (2H, t, $J$=4.3 Hz, $CH_2$), 4.08 (2H, t, $J$=4.3 Hz, $CH_2$), 5.74 (2H, s, $CH_2$), 7.30 (1H, t, $J$=7.3 Hz, H-5), 7.36 (1H, t, $J$=7.3 Hz, H-6), 7.70 (1H, d, $J$=7.3 Hz, H-7), 8.15 (1H, d, $J$=7.3 Hz, H-4), 8.46 (1H, s, H-2), 9.99 (1H, s, CHO) | 20.50 (q), 62.72 (t), 66.16 (t), 76.11 (t), 115.58 (d), 117.91 (s), 121.15 (d), 122.99 (s), 123.99 (d), 124.93 (d), 136.98 (s), 141.12 (d), 170.26 (s), 185.29 (d) |
| **6d** [b] | 62 | 101 [c] (C) | 1738 (CO) | 1.94 (1H, s, $CH_3$), 3.45 (2H, t, $J$=4.4 Hz, $CH_2$), 4.05 (2H, t, $J$=4.4 Hz, $CH_2$), 5.42 (2H, s, $CH_2$), 7.24 (1H, dt, $J$=7.1, 1.5 Hz, H-5), 7.31 (1H, dt, $J$=7.1, 1.5 Hz, H-6), 7.43–7.54 (6H, m, $C_6H_5$ and H-7), 7.60 (1H, dd, $J$=7.1, 1.5 Hz, H-4); | 20.68 (q), 62.95 (t), 65.80 (t), 73.74 (t), 92.74 (s), 110.35 (d), 119.42 (d), 121.44 (d), 123.53 (d), 127.60 (s), 128.45 (d), 128.93 (d), 129.77 (s), 130.78 (d), 136.30 (s), 137.84 (s), 170.71 (s) |
| **6e** | 71 | 93–95 (D) | 1736 (CO) | 1.89 (1H, s, $CH_3$), 3.51 (2H, t, $J$=4.4 Hz, $CH_2$), 3.90 (2H, t, $J$=4.4 Hz, $CH_2$), 5.45 (2H, s, $CH_2$), 7.46 (1H, dt, $J$=6.5, 1.0 Hz, H-5), 7.51 (1H, dt, $J$=6.5, 1.0 Hz, H-6), 7.60 (5H, s, $C_6H_5$), 7.87 (1H, dd, $J$=6.5, 1.0 Hz, H-7), 8.22 (1H, dd, $J$=6.5, 1.0 Hz, H-4) | 20.46 (q), 62.60 (t), 66.09 (t), 73.25 (t), 112.16 (d), 120.03 (d), 120.47 (s), 124.51 (d), 124.94 (d), 128.24 (2s), 128.38 (d), 129.97 (d), 130.18 (d), 134.44 (s), 143.09 (s), 170.09 (s) |
| **6f** | 75 | 164 [c] (E) | 1732 (CO) | 1.86 (3H, s, $CH_3$), 3.40 (2H, t, $J$=4.0 Hz, $CH_2$), 3.89 (2H, t, $J$=4.0 Hz, $CH_2$), 5.86 (2H, s, $CH_2$), 7.29 (1H, t, $J$=7.3 Hz, H-5), 7.39 (1H, t, $J$=7.3 Hz, H-6), 7.50 (1H, t, $J$=7.9 Hz, H-4′), 7.57 (1H, d, $J$=7.3 Hz, H-7), 7.77 (1H, d, $J$=7.3 Hz, H-4), 7.87 (1H, d, $J$=7.9 Hz, H-6′), 8.03 (1H, t, $J$=7.9 Hz, H-5′), 8.79 (1H, d, $J$=7.9 Hz, H-3′) | 20.63 (q), 62.65 (t), 65.56 (t), 73.19 (t), 92.64 (s), 111.43 (d), 119.09 (d), 121.57 (d), 123.48 (d), 124.21 (d), 126.36 (d), 126.57 (s), 135.49 (s), 136.63 (s), 136.99 (d), 148.89 (s), 149.70 (d), 170.11 (s) |
| **6g** | 59 | 64–65 (A) | 1734 (CO) | 1.85 (3H, s, $CH_3$), 3.49 (2H, t, $J$=4.5 Hz, $CH_2$), 3.93 (2H, t, $J$=4.5 Hz, $CH_2$), 5.60 (2H, s, $CH_2$), 7.49 (1H, dt, $J$=6.1, 1.1 Hz, H-5), 7.54 (1H, dt, $J$=6.1, 1.1 Hz, H-6), 7.60 (1H, dt, $J$=7.8, 1.7 Hz, H-4′), 7.87 (1H, dd, $J$=6.1, 1.1 Hz, H-7), 7.89 (1H, dd, $J$=7.8, 1.7 Hz, H-6′), 8.05 (1H, dt, $J$=7.8, 1.7 Hz, H-5′), 8.22 (1H, dd, $J$=6.1, 1.1 Hz, H-4), 8.81 (1H, dd, $J$=7.8, 1.7 Hz, H-3′) | 20.46 (q), 62.51 (t), 66.04 (t), 73.50 (t), 112.52 (d), 120.13 (2d), 124.79 (s), 124.80 (d), 125.30 (d), 126.60 (s), 127.08 (d), 134.38 (s), 136.92 (d), 140.61 (s), 147.72 (s), 149.63 (d), 170.09 (s) |
| **3a** | 70 | 56–57 (A) | 3472 (OH), 2220 (CN) | 3.41–3.51 (4H, m, 2×$CH_2$), 4.72 (1H, t, $J$=5.9 Hz, OH), 5.71 (2H, s, $CH_2$), 7.33 (1H, t, $J$=7.4 Hz, H-5), 7.40 (1H, t, $J$=7.4 Hz, H-6), 7.66 (1H, d, $J$=7.4 Hz, H-7), 7.76 (1H, d, $J$=7.4 Hz, H-4), 8.45 (1H, s, H-2) | 59.91 (t), 70.13 (t), 76.17 (t), 84.85 (s), 112.03 (d), 115.65 (s), 118.81 (d), 122.52 (d), 123.92 (d), 127.27 (s), 135.22 (s), 137.40 (d) |
| **3b** | 72 | 85–86 (B) | 3366 (OH), 1645 (CO) | 2.48 (3H, s, $CH_3$), 3.42–3.54 (4H, m, 2×$CH_2$), 4.72 (1H, t, $J$=5.3 Hz, OH), 5.69 (2H, s, $CH_2$), 7.25 (1H, dt, $J$=7.7, 1.5 Hz, H-5), 7.30 (1H, dt, $J$=7.7, 1.5 Hz, H-6), 7.65 (1H, dd, $J$=7.7, 1.5 Hz, H-7), 8.23 (1H, dd, $J$=7.7, 1.5 Hz, H-4), 8.49 (1H, s, H-2) | 27.30 (q), 59.96 (t), 70.01 (t), 76.15 (t), 111.14 (d), 116.55 (s), 121.59 (d), 122.44 (d), 123.22 (d), 126.04 (s), 136.61 (s), 137.38 (d), 184.42 (s) |

(*continued*)

Table 2 (*continued*)

| Comp. | Yield (%) | M.p. (°C) [a] | IR ($cm^{-1}$) | NMR [$(CD_3)_2SO$] [b] δ (ppm) | |
|---|---|---|---|---|---|
| | | | | $^1H$ | $^{13}C$ |
| **3c** | 70 | 101–102 (B) | 3412 (OH), 1658 (CO) | 3.41–3.54 (4H, m, 2×$CH_2$), 4.74 (1H, t, $J$=4.8 Hz, OH), 5.73 (2H, s, $CH_2$), 7.30 (1H, dt, $J$=7.2, 1.8 Hz, H-5), 7.36 (1H, dt, $J$=7.2, 1.8 Hz, H-6), 7.71 (1H, dd, $J$=7.2, 1.8 Hz, H-7), 8.16 (1H, dd, $J$=7.2, 1.8 Hz, H-4), 8.46 (1H, s, H-2), 9.99 (1H, s, CHO) | 59.94 (t), 70.08 (t), 76.29 (t), 111.58 (d), 117.81 (s), 121.11 (d), 122.94 (d), 123.96 (d), 124.87 (s), 136.99 (s), 141.16 (d), 185.08 (d) |
| **3d** | 80 | 95 (A) | 3296 (OH) | 3.34 (2H, t, $J$=4.0 Hz, $CH_2$), 3.38–3.43 (2H, m, $CH_2$), 4.66 (1H, t, $J$=4.0 Hz, OH), 5.49 (2H, s, $CH_2$), 7.25 (1H, t, $J$=7.3 Hz, H-5), 7.34 (1H, t, $J$=7.3 Hz, H-6), 7.49–7.57 (5H, m, $C_6H_5$), 7.59 (1H, d, $J$=7.3 Hz, H-7), 7.73 (1H, d, $J$=7.3 Hz, H-4) | 59.94 (t), 69.84 (t), 73.42 (t), 91.30 (s), 111.22 (d), 118.54 (d), 121.35 (d), 123.47 (d), 126.62 (s), 128.57 (d), 129.03 (s), 129.45 (d), 130.66 (d), 136.30 (s), 137.78 (s) |
| **3e** | 85 | 74–75 (A) | 3383 (OH) | 3.33–3.37 (4H, m, 2x$CH_2$), 4.66 (1H, t, $J$=4.9 Hz, OH), 5.44 (2H, s, $CH_2$), 7.45–7.51 (2H, m, H-5 and H-6), 7.60 (5H, s, $C_6H_5$), 7.88 (1H, dd, $J$=7.4, 2.0 Hz, H-7), 8.21 (1H, dd, $J$=7.4, 2.0 Hz, H-4) | 59.80 (t), 70.25 (t), 73.52 (t), 112.26 (d), 120.04 (d), 120.50 (s), 124.53 (d), 124.96 (d), 128.32 (s), 128.41 (d), 129.98 (d), 130.29 (d), 134.51 (s), 134.61 (s), 143.18 (s) |
| **3f** | 60 | 64–65 (A) | 3375 (OH) | 3.14–3.19 (2H, m, $CH_2$), 3.25 (2H, t, $J$=4.4 Hz, $CH_2$), 4.56 (1H, t, $J$=5.2 Hz, OH), 5.86 (2H, s, $CH_2$), 7.28 (1H, t, $J$=7.4 Hz, H-5), 7.38 (1H, t, $J$=7.4 Hz, H-6), 7.52 (1H, t, $J$=7.4 Hz, H-4′), 7.56 (1H, d, $J$=7.4 Hz, H-7), 7.77 (1H, d, $J$=7.4 Hz, H-6′), 7.87 (1H, d, $J$=7.4 Hz, H-4), 8.03 (1H, t, $J$=7.4 Hz, H-5′), 8.80 (1H, d, $J$=7.4 Hz, H-3′) | 59.75 (t), 69.69 (t), 73.32 (t), 92.47 (s), 111.44 (d), 119.02 (d), 121.48 (d), 123.46 (d), 124.14 (d), 126.37 (d), 126.49 (s), 135.61 (s), 136.63 (s), 136.98 (d), 148.97 (s), 149.67 (d) |
| **3g** [b] | 80 | 127–128 (B) | 3288 (OH) | 2.94 (1H, t, $J$=6.5 Hz, OH), 3.39–3.43 (2H, m, $CH_2$), 3.50 (2H, t, $J$=4.4 Hz, $CH_2$), 5.49 (2H, s, $CH_2$), 7.43 (2H, dt, $J$=6.6, 1.1 Hz, H-5 and H-6), 7.45 (1H, dt, $J$=7.7, 1.6 Hz, H-4′), 7.58 (1H, dd, $J$=6.6, 1.1 Hz, H-7), 7.65 (1H, dd, $J$=7.7, 1.6 Hz, H-6′), 7.87 (1H, dt, $J$=7.7, 1.6 Hz, H-5′), 8.36 (1H, dd, $J$=6.6, 1.1 Hz, H-4), 8.75 (1H, dd, $J$=7.7, 1.6 Hz, H-3′) | 61.14 (t), 69.99 (t), 74.00 (t), 111.11 (d), 120.82 (s), 121.35 (d), 124.51 (d), 124.79 (d), 125.50 (d), 127.24 (d), 134.78 (2s), 136.70 (d), 139.49 (s), 148.08 (s), 149.56 (d) |
| **3h** | 75 | 137–138 (F) | 3239–3153 (broad, OH and $NH_2$) | 3.26–3.32 (2H, m, $CH_2$), 3.37 (2H, t, $J$=5.4 Hz, $CH_2$), 4.28 (2H, s, $NH_2$), 4.57 (1H, t, $J$=5.4 Hz, OH), 5.39 (2H, s, $CH_2$), 7.03 (1H, dt, $J$=7.8, 1.5 Hz, H-5), 7.16 (1H, dt, $J$=7.8, 1.5 Hz, H-6), 7.33 (1H, dt, $J$=7.3, 1.5 Hz, H-4′), 7.48 (2H, dt, $J$=7.3, 1.5 Hz, H-3′ and H-5′), 7.51 (1H, dd, $J$=7.3, 1.5 Hz, H-2′ and H-6′), 7.59 (1H, dd, $J$=7.8, 1.5 Hz, H-7), 7.67 (1H, dd, $J$=7.8, 1.5 Hz, H-4) | 60.04 (t), 69.50 (t), 73.15 (t), 110.07 (d), 118.31 (d), 118.70 (d), 121.07 (s), 122.20 (s), 122.32 (d), 123.81 (s), 126.53 (d), 128.66 (d), 129.23 (d), 131.49 (s), 136.35 (s) |
| **3i** | 66 | 89–90 (F) | 3371 and 3287 ($NH_2$), 3200 (OH) | 3.37–3.47 (4H, m, 2×$CH_2$), 4.63 (1H, t, $J$=4.1 Hz, OH), 5.58 (2H, s, $NH_2$), 5.62 (2H, s, $CH_2$), 7.04 (1H, dt, $J$=7.6, 1.7 Hz, H-5), 7.16 (1H, dt, $J$=7.6, 1.7 Hz, H-6), 7.24 (1H, dt, $J$=6.9, 1.1 Hz, H-4′), 7.54 (1H, dd, $J$=7.6, 1.7 Hz, H-7), 7.74 (1H, dd, $J$=7.6, 1.7 Hz, H-4), 7.80 (1H, dd, $J$=6.9, 1.1 Hz, H-6′), 7.84 (1H, dt, $J$=6.9, 1.1 Hz, H-5′), 8.64 (1H, dd, $J$=6.9, 1.1 Hz, H-3′) | 60.13 (t), 69.56 (t), 74.19 (t), 110.49 (d), 117.93 (s), 118.92 (d), 119.24 (d), 119.31 (d), 121.24 (d), 121.71 (s), 124.16 (d), 129.83 (s), 136.67 (d), 138.46 (s), 149.07 (d), 152.27 (s) |

[a] Eluant or recrystallization solvent: A, dichloromethane (DCM)/ethyl acetate 9:1; B, DCM/ethyl acetate 8:2; C, DCM/petroleum ether (b.p. 40–60°C) 7:3; D, DCM; E, DCM/ethyl acetate 95:5; F, ethanol.

[b] NMR solvent: $CDCl_3$.

[c] Uncrystallizable oil, b.p.

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