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Glycosidopyrroles
Part 1. Acyclic derivatives: 1-(2-hydroxyethoxy)methylpyrroles as potential anti-viral agents [1]

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Abstract

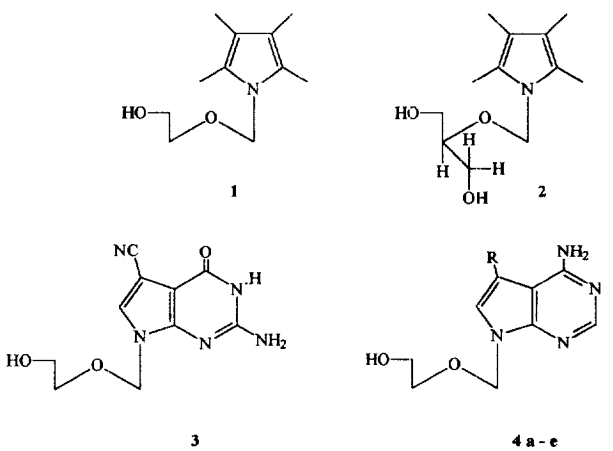
Acyclic glycosidopyrroles of type **1**, synthesized in good overall yields, were evaluated for anti-viral activity. Compound **10i** was found to inhibit the HIV-1 replication at concentrations that were very close to those cytotoxic for MT-4 cells. Compounds **10a,f,i** inhibited both strains HSV-1 and HSV-2 at concentrations slightly below those cytotoxic for Vero cells. However for this series of glycosidopyrroles some relationship between calculated log *P* values and the observed cytotoxicity was found.

Keywords: Anti-viral agents; Acyclic glycosidopyrroles; 1-(2-Hydroxyethoxy)methylpyrroles

1. Introduction

Continuing our studies on biologically active compounds which contain the pyrrole moiety, recently we became interested in the synthesis of new glycosidopyrroles as potential anti-viral agents. In particular, glycosidopyrroles of type **1** or **2**, being related to acyclovir and ganciclovir because of the acyclic moiety, could be considered more simple carbon bioisosters of the above anti-herpes drugs and, therefore, could be endowed with some anti-viral activity. In fact, when investigated as anti-viral agents, some deaza analogues of acyclovir, namely pyrrolo[2,3-*d*]pyrimidine derivatives of type **3** and **4**, have been found endowed with anti-herpes simplex virus type 1 (HSV-1) and anti-human cytomegalovirus (HCMV) activity [1–3]. Moreover they have also shown anti-human immunodeficiency virus (HIV) activity [4] (Fig. 1).

In this paper we report the synthesis and a wide biological evaluation of derivatives of type **1**, in which one of the α positions of the pyrrole ring always bears a phenyl group.



a, R = Cl; b, R = Br; c, R = I; d, R = CN; e, R = $CSNH_2$

Fig. 1. Structure of derivatives **1–4**.

2. Chemistry

The synthesis of 1-(2-hydroxyethoxy)methylpyrroles of type **1** was achieved according to Scheme 1. The 1H-pyrroles **5a–i**, suitably substituted at positions 3 and/or 4 with at least

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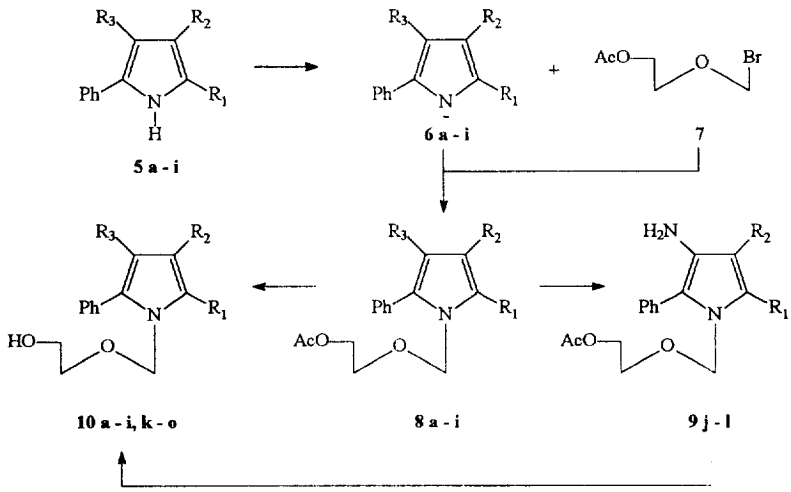

	R^1	R^2	R^3
a	Me	COOEt	Cl
b	Me	COOEt	NO_2
c	Ph	H	NO_2
d	Ph	Br	Br
e	Ph	COOEt	Br
f	Ph	COOEt	NO_2
g	Ph	CN	NO_2
h	Ph	Ph	Br
i	Ph	Ph	NO_2
j	Me	COOEt	NH_2
k	Ph	COOEt	NH_2
l	Ph	CN	NH_2
m	Ph	Ph	NH_2
n	Ph	COOH	NO_2
o	Ph	Ph	N_3

Scheme 1.

one electron-withdrawing group, were reacted with sodium hydride in acetonitrile to give the corresponding sodium salts **6**. The latter compounds were condensed with (2-acetoxyethoxy)methyl bromide (**7**), which was prepared from dioxolane and acetyl bromide [5]. 1-(2-Acetoxyethoxy)methyl derivatives of type **8** were isolated in yields from moderate to good following reactions carried out at room temperature that were completed within 2 h.

Compounds **8b,f,g** bearing a nitro group in R_3 were reduced, either catalytically or with iron and acetic acid in the case of **8b**, to give the corresponding 3-amino derivatives **9j–l** in good yields.

In all cases, removal of the protecting group with sodium methoxide in methanol, at room temperature for 20–90 min, gave derivatives **10a–e,g–i,k,l** in yields from moderate to good. Only in the case of derivative **8f** was the hydrolysis carried out with sodium ethoxide in ethanol to avoid transesterification.

The amino derivative **10m** was obtained by reduction with zinc and ammonium chloride of the corresponding nitropyrrole **10i**.

Further chemical modification of the R_3 substituent allowed the preparation of a few other 1-(2-hydroxyethoxy)methyl derivatives. In particular, compound **10o** was prepared in good yields by diazotization of the amino derivative **10m**, followed by treatment with sodium azide. Derivatives **10n** and **10c** were obtained upon hydrolysis and decarboxylation of the ester function in derivative **8f** respectively. Derivative **10c** was identical in every respect to the product obtained directly from the 1H-pyrrole **5c**.

3. Biology

The cytotoxicity of glycosidopyrrole derivatives was evaluated in vitro in $CD4^+$ lymphocytes (MT-4) and fibroblastoid cells (Vero). Compounds were also evaluated for anti-viral activity against human immunodeficiency virus (HIV) in MT-4 and herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2) in Vero cells.

The anti-bacterial activity was tested against Gram positive (*Staphylococcus aureus*, group D *Streptococcus*), Gram negative (*Pseudomonas aeruginosa*, *Salmonella sp.*), and acid

fast (*Mycobacterium avium*, *Myc. turberculosis*) microorganisms, whereas the anti-mycotic activity was evaluated against *Candida albicans*, *C. parapsilosis*, and *C. paratropicalis*, *Thricophyton mentagrophytes*, *Aspergillus fumigatus* and *Criptococcus neoformans*.

4. Results and discussion

The cytotoxicity of test compounds, evaluated by measuring the number of viable cells, was found to range between 15 and 300 μM. Since no significant differences were found between the two cell lines, only the data obtained with MT-4 cells are shown (Table 1). The highest cytotoxicity correlates with the presence of phenyl rings at positions 2 and 3, no matter which is the substituent R_3. Glycosidopyrroles of the series **10** and homologous acetoxyethoxy derivatives of the series **8** and **9** showed the same cytotoxicity, with the sole exception of compounds **i**.

When evaluated for their capability to prevent the virus-induced cytopathogenicity in cell cultures infected at low multiplicity of infection, only compound **10i** was found to inhibit the HIV-1 multiplication. This occurred at concentrations that were close to those cytotoxic for MT-4 cells.

Plaque reduction assays revealed that most of the compounds were inactive against both HSV-1 and HSV-2 with the exception of **10a**,**f**,**i** that inhibited both strains at concentrations slightly below those cytotoxic for Vero cells.

In Table 1 we also report the parameters chosen to define the lipophilicity of title compounds, i.e., the R_M (measured) and the log P (calculated) values. Actually, a good correlation was found between these two sets of data, expecially in the case of the unprotected derivatives. In fact, regression analysis of the data for compounds **10a–i**, **k–m** ($n=12$) gives the following regression equation:

$$R_M = 0.115(\log P) - 0.336 \quad (1)$$

with $r=0.927$; $r^2=0.860$; $cv=0.822$; residual sum of squares = 0.034; predictive sum of squares = 0.044.

Therefore, we could use these log P values to explore the structure–cytotoxicity relationship. Some relationship was found between the calculated log P values and the observed cytotoxicity (Eq. (2)).

$$-\log CC_{50} = 0.236(\log P) - 2.797 \quad (2)$$

with $n=15$; $r=0.866$; $r^2=0.749$; $cv=0.680$; residual sum of squares = 0.365; predictive sum of squares = 0.466.

Table 1
Cytotoxicity, anti-viral activity [a] and lipophilicity indexes of pyrrole derivatives

Compound	CC_{50} [b]	EC_{50} [c]			R_M	log P
		HIV-1	HSV-1	HSV-2		
8a	82	>82	>200	200	0.246	3.158
8b	169	>169	>169	>169	0.135	2.593
8c	37	>37	37	>66	0.335	4.039
8d	23	>23	>23	>23	0.527	5.669
8e	47	>47	>47	>47	0.406	4.958
8f	96	>96	>96	>96	0.269	4.112
8g	>300	>300	>300	>300	0.196	4.075
8h	16	>16	>16	>16	0.619	6.562
8i	>300	>300	>300	>300	0.385	5.724
9j	nd	nd	nd	nd	0.610	1.856
9l	>300	>300	>300	>300	0.112	3.339
10a	111	>111	103	100	0.078	3.028
10b	>300	>300	>300	>300	−0.003	2.454
10c	46	>46	>46	>46	0.156	3.910
10d	51	>51	>51	>51	0.353	4.749
10e	64	>64	>64	>64	0.237	4.821
10f	163	>163	200	200	0.065	3.983
10g	>300	>300	>300	>300	0.049	3.946
10h	15	>15	>15	>15	0.443	6.433
10i	43	37	200	40	0.225	5.595
10k	nd	nd	nd	nd	0.033	3.246
10l	>300	>300	>300	>300	−0.047	3.209
10m	42	>42	>42	>42	0.224	4.858
10n	>300	>300	>300	>300	−0.984	3.609
10o	65	>65	>65	>65	0.459	nc

[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) or plaque number (HSV-1 and HSV-2) by 50%.
nd: not determined; nc: not calculated.

As can be seen, compounds with high lipophilicity were also those with higher cytotoxicity and higher anti-viral activity. This could be due to the fact that lipophilic compounds easily penetrate through the cell membrane.

None of the compounds showed anti-bacterial or anti-fungal activity.

5. Experimental

5.1. Chemistry

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected. IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured at 250 and 62.8 MHz, respectively, in $(CD_3)_2SO$ solution, unless otherwise specified, using a Bruker AC-E series 250 MHz spectrometer (TMS as internal reference). Mass spectra were obtained with a HP 5890 Series II and HP 5989A-GC/MS apparatus. Column chromatography was performed with Merck silica gel 230-400 Mesh ASTM; the following mixtures of solvents were used as eluents: petroleum ether (b.p. 40–60°C):ethyl acetate 8:2 (A), 7:3 (B), 6:4 (C), 2:8 (D); dichloromethane (E); dichloromethane:petroleum ether (b.p. 40–60°C) 8:2 (F); dichloromethane:ethyl acetate 9:1 (G). Analyses indicated by the symbols of the elements or functions were within ±0.4% of theoretical values.

1H-Pyrrole derivatives **5** were prepared according to the procedures reported in the literature: **5a,e,h** [6]; **5b,f,g** [7]; **5c,i** [8]; **5d** [9].

1-(2-Acetoxyethoxy)methyl bromide (**7**) was prepared from 1,3-dioxolane and acetyl bromide, according to Ref. [5].

5.1.1. General method for the preparation of 1-(2-acetoxyethoxy)methylpyrroles 8a–i

Sodium hydride (6 mmol, 55% oil dispersion) was added at room temperature to a solution of pyrroles **5a–i** (5 mmol) in acetonitrile (30 ml). A solution of **7** (10–15 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 (TLC monitorage). The solvent was evaporated under reduced pressure, and the residue was washed with water, extracted with dichloromethane, dried over sodium sulfate. Removal of the solvent in vacuo gave a crude residue which was purified by column chromatography.

*1-(2-Acetoxyethoxy)methyl-4-chloro-3-ethoxycarbonyl-2-methyl-5-phenylpyrrole (**8a**)*, eluent A, yield 78%, was obtained as an oil, b.p. 230°C. IR: 1736 (CO), 1697 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$, ppm): 1.38 (3H, t, J=7.1 Hz, CH_3), 2.02 (3H, s, CH_3), 2.63 (3H, s, CH_3), 3.41 (2H, t, J=4.6 Hz, CH_2), 4.07 (2H, t, J=4.6 Hz, CH_2), 4.33 (2H, q, J=7.1 Hz, CH_2), 5.14 (2H, s, CH_2), 7.37–7.48 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm): 10.55 (q), 14.33 (q), 20.70 (q), 59.85 (t), 62.80 (t), 65.63 (t), 73.46 (t), 111.05 (s), 128.49 (d), 128.55 (d), 129.29 (2s), 130.73 (s), 130.85 (d), 136.40 (s), 164.13 (s), 170.63 (s). *m/z* 379/381. *Anal.* $C_{19}H_{22}ClNO_5$ (C, H, Cl, N).

*1-(2-Acetoxyethoxy)methyl-3-ethoxycarbonyl-2-methyl-4-nitro-5-phenylpyrrole (**8b**)*, eluent C, yield 52%, was obtained as an oil, b.p. 208°C. IR: 1732 and 1711 (CO), 1510 and 1377 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, ppm): 1.31 (3H, t, J=7.1 Hz, CH_3), 2.01 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.41 (2H, t, J=4.6 Hz, CH_2), 4.06 (2H, t, J=4.6 Hz, CH_2), 4.30 (2H, q, J=7.1 Hz, CH_2), 5.05 (2H, s, CH_2), 7.24–7.46 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm): 10.61 (q), 13.96 (q), 20.69 (q), 60.95 (t), 62.66 (t), 66.16 (t), 73.49 (t), 109.49 (s), 127.23 (s), 128.62 (d), 129.92 (d), 130.75 (s), 130.76 (d), 132.15 (s), 134.46 (s), 163.08 (s), 170.63 (s). *m/z* 390. *Anal.* $C_{19}H_{22}N_2O_7$ (C, H, N).

*1-(2-Acetoxyethoxy)methyl-2,5-diphenyl-3-nitropyrrole (**8c**)*, eluent E, yield 56%, was obtained as an oil, b.p. 265°C. IR: 1738 (CO), 1499 and 1371 (NO_2) cm^{-1}. ^{1}H NMR (ppm): 1.99 (3H, s, CH_3), 3.33 (2H, t, J=4.5 Hz, CH_2), 3.98 (2H, t, J=4.5 Hz, CH_2), 4.98 (2H, s, CH_2), 7.00 (1H, s, CH), 7.49–7.68 (10, H, m, 2×C_6H_5). ^{13}C NMR (ppm): 20.78 (q), 62.78 (t), 65.74 (t), 74.04 (t), 105.44 (d), 128.50 (d), 128.80 (s), 128.89 (d), 129.07 (2d), 129.76 (d), 130.48 (s), 130.85 (d), 133.92 (s), 134.68 (s), 135.59 (s), 170.33 (s). *m/z* 380. *Anal.* $C_{21}H_{20}N_2O_5$ (C, H, N).

*1-(2-Acetoxyethoxy)methyl-3,4-dibromo-2,5-diphenylpyrrole (**8d**)*, eluent F, yield 40%, was recrystallized from ethanol, m.p. 87°C. IR: 1734 (CO) cm^{-1}. ^{1}H NMR (ppm): 2.03 (3H, s, CH_3), 3.29 (2H, t, J=4.4 Hz, CH_2), 3.97 (2H, t, J=4.4 Hz, CH_2), 5.03 (2H, s, CH_2), 7.51–7.63 (10H, m, 2×C_6H_5). ^{13}C NMR (ppm): 20.77 (q), 62.79 (t), 65.44 (t), 74.83 (t), 99.99 (s), 128.75 (d), 128.98 (d), 129.98 (s), 130.59 (d), 132.90 (s), 170.31 (s). *m/z* 491/493/495. *Anal.* $C_{21}H_{19}Br_2NO_3$ (C, H, Br, N).

*1-(2-Acetoxyethoxy)methyl-4-bromo-2,5-diphenyl-3-ethoxycarbonylpyrrole (**8e**)*, eluent A, yield 84%, was recrystallized from ethanol, m.p. 90°C. IR: 1738 (CO), 1705 (CO) cm^{-1}. ^{1}H NMR (ppm): 0.99 (3H, t, J=7.1 Hz, CH_3), 2.02 (3H, s, CH_3), 3.26 (2H, t, J=4.5 Hz, CH_2), 3.95 (2H, t, J=4.5 Hz, CH_2), 4.04 (2H, q, J=7.1 Hz, CH_2), 4.96 (2H, s, CH_2), 7.49–7.62 (10H, m, 2×C_6H_5). ^{13}C NMR (ppm): 13.80 (q), 20.74 (q), 59.61 (t), 62.77 (t), 65.55 (t), 74.15 (t), 97.27 (s), 113.47 (s), 128.10 (d), 128.67 (d), 128.94 (d), 129.00 (d), 129.80 (s), 130.71 (s), 130.81 (d), 130.95 (d), 133.38 (s), 138.95 (s), 162.83 (s), 170.29 (s). *m/z* 485/487. *Anal.* $C_{24}H_{24}BrNO_5$ (C, H, Br, N).

*1-(2-Acetoxyethoxy)methyl-2,5-diphenyl-3-ethoxycarbonyl-4-nitropyrrole (**8f**)*, eluent B, yield 80%, was obtained as an oil, b.p. 210°C. IR: 1732 (broad CO), 1508 and 1339 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, ppm): 1.14 (3H, t, J=7.1 Hz, CH_3), 2.03 (3H, s, CH_3), 3.30 (2H, t, J=4.5 Hz, CH_2), 4.03 (2H, t, J=4.5 Hz, CH_2), 4.17 (2H, q, J=7.1 Hz, CH_2), 4.86 (2H, s, CH_2), 7.43–7.57 (10H, m, 2×C_6H_5). ^{13}C NMR ($CDCl_3$, ppm): 13.66 (q), 20.70 (q), 61.17 (t), 62.77 (t), 65.93 (t), 73.70 (t), 95.22 (s), 111.52 (s), 127.36 (s),

128.28 (d), 128.41 (d), 129.56 (d), 129.93 (d), 130.62 (d), 130.67 (d), 130.80 (s), 133.45 (s), 135.60 (s), 162.82 (s), 170.31 (s). *m/z* 452. *Anal.* $C_{24}H_{24}N_2O_7$ (C, H, N).

*1-(2-Acetoxyethoxy)methyl-3-cyano-2,5-diphenyl-4-nitropyrrole (**8g**)*, eluent C, yield 95%, was recrystallized from ethanol, m.p. 122°C. IR: 2235 (CN), 1736 (CO), 1510 and 1339 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, ppm): 2.04 (3H, s, CH_3), 3.37 (2H, t, $J=4.5$ Hz, CH_2), 4.08 (2H, t, $J=4.5$ Hz, CH_2), 4.90 (2H, s, CH_2), 7.50–7.69 (10H, m, $2\times C_6H_5$). ^{13}C NMR ($CDCl_3$, ppm): 20.74 (q), 62.75 (t), 66.32 (t), 74.23 (t), 90.72 (s), 113.09 (s), 126.74 (s), 126.88 (s), 128.63 (d), 128.68 (s), 129.16 (d), 129.91 (d), 130.51 (d), 130.55 (d), 130.71 (d), 136.09 (s), 142.90 (s), 170.48 (s). *m/z* 405. *Anal.* $C_{22}H_{19}N_3O_5$ (C, H, N).

*1-(2-Acetoxyethoxy)methyl-3-bromo-2,4,5-triphenylpyrrole (**8h**)*, eluent A, yield 72%, was recrystallized from ethanol, m.p. 79°C. IR: 1736 (CO) cm^{-1}. ^1H NMR (ppm): 2.06 (3H, s, CH_3), 3.35 (2H, t, $J=4.6$ Hz, CH_2), 4.03 (2H, t, $J=4.5$ Hz, CH_2), 5.02 (2H, s, CH_2), 7.23–7.71 (15H, m, $3\times C_6H_5$). ^{13}C NMR (ppm): 20.81 (q), 62.89 (t), 65.33 (t), 74.31 (t), 98.35 (s), 122.98 (s), 126.68 (d), 128.10 (d), 128.25 (d), 128.50 (d), 128.57 (d), 128.65 (d), 130.24 (s), 130.45 (d), 130.70 (d), 130.91 (s), 131.02 (d), 132.42 (s), 132.50(s), 133.91(s), 170.36(s). *m/z* 489/491. *Anal.* $C_{27}H_{24}BrNO_3$ (C, H, Br, N).

*1-(2-Acetoxyethoxy)methyl-3-nitro-2,4,5-triphenylpyrrole (**8i**)*, eluent E, yield 51%, was recrystallized from ethanol, m.p. 127°C. IR: 1734 (CO), 1499 and 1339 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, ppm): 2.05 (3H, s, CH_3), 3.33 (2H, t, $J=4.6$ Hz, CH_2), 4.06 (2H, t, $J=4.6$ Hz, CH_2), 4.90 (2H, s, CH_2), 7.48–7.63 (15H, m, $3\times C_6H_5$). ^{13}C NMR ($CDCl_3$, ppm): 20.75 (q), 62.90 (t), 65.77 (t), 73.83 (t), 119.37 (s), 126.88 (d), 127.71 (d), 128.25 (d), 128.27 (d), 128.53 (d), 128.71 (s), 129.50 (d), 129.59 (2s), 130.33 (d), 130.78 (d), 131.16 (d), 132.02 (s), 132.27 (s), 134.20 (s), 170.57 (s). *m/z* 456. *Anal.* $C_{27}H_{24}N_2O_5$ (C, H, N).

*5.1.2. Preparation of 1-(2-acetoxyethoxy)methyl-3-aminopyrroles **9j–l***

(a) Method A

A solution of nitro derivatives **8f,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 a residue which was purified by column chromatography.

*1-(2-Acetoxyethoxy)methyl-3-amino-2,5-diphenyl-4-ethoxycarbonylpyrrole (**9k**)*, eluent A, yield 75% (*m/z* 422), was directly reacted with sodium methoxide to give the deprotected derivative without further purification.

*1-(2-Acetoxyethoxy)methyl-3-amino-4-cyano-2,5-diphenylpyrrole (**9l**)*, eluent C, yield 73%, m.p. 60–62°C. IR: 3447 and 3422 (NH_2), 2216 (CN), 1736 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, ppm): 2.06 (3H, s, CH_3), 3.42 (2H, t, $J=4.5$ Hz, CH_2), 3.48 (2H, s, NH_2), 4.13 (2H, t, $J=4.5$ Hz, CH_2), 4.97 (2H, s, CH_2), 7.26–7.67 (10H, m, $2\times C_6H_5$). ^{13}C NMR ($CDCl_3$, ppm): 20.80 (q), 62.99 (t), 65.36 (t), 74.27 (t), 115.84 (s), 127.89 (d), 128.87 (d), 128.90 (s), 129.07 (s), 129.09 (d), 129.17 (d), 129.23 (s), 129.38 (d), 129.56 (d), 129.96 (s), 131.77 (s), 139.72 (s), 170.70 (s). *m/z* 375. *Anal.* $C_{22}H_{21}N_3O_3$ (C, H, N).

(b) Method B

Iron powder (50 mg) was added to a solution of nitro derivative **8b** (5 mmol) in acetic acid (30 ml). The mixture was kept at 60°C in a steam bath for 16 h. The reaction mixture was cooled, poured onto crushed ice and extracted with dichloromethane. The organic layer, dried over sodium sulfate and evaporated under reduced pressure, gave a residue which was purified by column chromatography (eluent G) to give **9j**.

1-(2-acetoxyethoxy)methyl-3-amino-4-ethoxycarbonyl-2-phenyl-5-methylpyrrole (**9j**), yield 60%, oil, b.p. 265°C. IR: 3447 and 3358 (NH_2), 1736 (CO), 1682 (CO) cm^{-1}. ^1H NMR (ppm): 1.38 (3H, t, $J=7.1$ Hz, CH_3), 2.03 (3H, s, CH_3), 3.77 (2H, t, $J=4.6$ Hz, CH_2), 3.78 (3H, s, CH_3), 4.25 (2H, t, $J=4.6$ Hz, CH_2), 4.32 (2H, q, $J=7.1$ Hz, CH_2), 4.70 (2H, s, CH_2), 5.20 (2H, s, NH_2), 7.24–7.46 (5H, m, C_6H_5). ^{13}C NMR ppm: 11.66 (q), 14.50 (q), 20.85 (q), 59.40 (t), 63.46 (t), 65.54 (t), 72.98 (t), 125.89 (s), 126.95 (d) 128.51 (s), 128.97 (d), 129.77 (d) 130.95 (s), 131.06 (s), 134.93 (s), 166.11 (s), 170.95 (s). *m/z* 360. *Anal.* $C_{19}H_{24}N_2O_5$ (C, H, N).

*5.1.3. General method for the preparation of 1-(2-hydroxyethoxy)methylpyrroles **10a–e,g–i,k,l***

A solution of sodium methoxide (5 mmol) in methanol (10 ml) was added dropwise to a solution of compounds **8a–e,g–i** or **9j–l** (5 mmol) in methanol (30 ml). The reactants were stirred at room temperature until disappearance of the starting materials (TLC monitorage). 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.

*4-Chloro-3-ethoxycarbonyl-1-(2-hydroxyethoxy)methyl-2-methyl-5-phenylpyrrole (**10a**)*, eluent A, yield 62%, was obtained as an oil, b.p. 192°C. IR: 3466 (broad OH), 1696 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, ppm): 1.38 (3H, t, $J=7.1$ Hz, CH_3), 2.62 (3H, s, CH_3), 3.30 (2H, t, $J=4.4$ Hz, CH_2), 3.60 (2H, t, $J=4.4$ Hz, CH_2), 3.86 (1H, s, OH), 4.33 (2H, q, $J=7.1$ Hz, CH_2), 5.15 (2H, s, CH_2), 7.36–7.49 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm): 11.69 (q), 14.40 (q), 60.00 (t), 61.42 (t), 69.22 (t), 73.69 (t), 111.09 (s), 128.60 (d), 128.65 (d), 129.38 (s), 129.44 (s), 130.80 (s), 130.92 (d), 136.41 (s), 164.34 (s). *m/z* 337/339. *Anal.* $C_{17}H_{20}ClNO_4$ (C, H, Cl, N).

*3-Ethoxycarbonyl-1-(2-hydroxyethoxy)methyl-2-methyl-4-nitro-5-phenylpyrrole (**10b**)*, eluent G, yield 48%, was obtained as an oil, b.p. 250°C. IR: 3464 (broad OH), 1713 (CO), 1510 and 1339 (NO_2) cm^{-1}. ^1H NMR (ppm): 1.25 (3H, t, $J=7.1$ Hz, CH_3), 2.50 (3H, s, CH_3), 3.26 (2H, t, $J=4.5$ Hz, CH_2), 3.34–3.43 (2H, m, CH_2), 4.25 (2H, q,

J = 7.1 Hz, CH_2), 4.67 (1H, t, J = 5.4 Hz, OH), 5.12 (2H, s, CH_2), 7.44–7.55 (5H, m, C_6H_5). ^{13}C NMR (ppm): 10.63 (q), 14.10 (q), 59.95 (t), 60.64 (t), 70.14 (t), 73.83 (t), 108.49 (s), 127.33 (s), 128.74 (d), 129.99 (d), 130.82 (d), 132.66 (s), 133.02 (s), 134.82 (s), 162.65 (s). *m/z* 348. *Anal.* $C_{17}H_{20}N_2O_6$ (C, H, N).

2,5-Diphenyl-1-(2-hydroxyethoxy)methyl-3-nitropyrrole (***10c***), eluent E, yield 65%, was obtained as an oil, b.p. 235°C. IR: 3543 (OH), 1485 and 1316 (NO_2) cm^{-1}. ^1H NMR (ppm): 3.20 (2H, t, J = 4.9 Hz, CH_2), 3.40–3.46 (2H, m, CH_2), 4.75 (1H, t, J = 5.4 Hz, OH), 5.03 (2H, s, CH_2), 7.05 (1H, s, CH), 7.52–7.76 (10, H, m, 2×C_6H_5). ^{13}C NMR (ppm): 59.94 (t), 69.95 (t), 74.30 (t), 105.35 (d), 128.50 (d), 128.83 (d), 129.07 (d), 129.12 (d), 129.72 (d), 130.54 (2s), 130.92 (d), 133.84 (s), 134.70 (s), 135.60 (s). *m/z* 338. *Anal.* $C_{19}H_{18}N_2O_4$ (C, H, N).

3,4-Dibromo-2,5-diphenyl-1-(2-hydroxyethoxy)methylpyrrole (***10d***), eluent B, yield 63%, m.p. 147°C. IR: 3588 (broad OH) cm^{-1}. ^1H NMR (ppm): 3.05 (2H, t, J = 5.0 Hz, CH_2), 3.20–3.34 (2H, m, CH_2), 4.61 (1H, t, J = 5.5 Hz, OH), 4.98 (2H, s, CH_2), 7.44–7.60 (10H, m, 2×C_6H_5). ^{13}C NMR (ppm): 59.91 (t), 69.71 (t), 74.13 (t), 99.84 (s), 128.73 (d), 128.91 (d), 130.07 (s), 130.66 (d), 132.89 (s). *m/z* 449/451/453. *Anal.* $C_{19}H_{17}Br_2NO_2$ (C, H, Br, N).

4-Bromo-2,5-diphenyl-3-ethoxycarbonyl-1-(2-hydroxyethoxy)methylpyrrole (***10e***), eluent A, yield 88%, was recrystallized from ethanol, m.p. 120°C. IR: 3586 (broad OH), 1703 (CO) cm^{-1}. ^1H NMR (ppm): 0.99 (3H, t, J = 7.1 Hz, CH_3), 3.07 (2H, t, J = 5.0 Hz, CH_2), 3.31–3.37 (2H, m, CH_2), 4.05 (2H, q, J = 7.1 Hz, CH_2), 4.65 (1H, t, J = 4.5 Hz, OH), 4.96 (2H, s, CH_2), 7.53–7.63 (10H, m, 2×C_6H_5). ^{13}C NMR (ppm): 13.81 (q), 59.59 (t), 59.88 (t), 69.79 (t), 74.44 (t), 97.15 (s), 113.37 (s), 128.08 (d), 128.65 (d), 128.87 (d), 128.93 (d), 129.87 (s), 130.78 (s), 130.85 (d), 131.01 (d), 133.37 (s), 138.93 (s), 162.89 (s). *m/z* 443/445. *Anal.* $C_{22}H_{22}BrNO_4$ (C, H, Br, N).

4-Cyano-2,5-diphenyl-1-(2-hydroxyethoxy)methyl-3-nitropyrrole (***10g***), eluent A, yield 60%, was recrystallized from ethanol, m.p. 215°C. IR: 3586 (OH), 2236 (CN), 1483 and 1339 (NO_2) cm^{-1}. ^1H NMR (ppm): 3.12 (2H, t, J = 4.7 Hz, CH_2), 3.32–3.38 (2H, m, CH_2), 4.70 (1H, t, J = 5.3 Hz, OH), 5.05 (2H, s, CH_2), 7.62–7.82 (10H, m, 2×C_6H_5). ^{13}C NMR (ppm): 64.78 (t), 75.40 (t), 79.85 (t), 94.67 (s), 118.63 (s), 132.03 (s), 132.26 (s), 133.64 (d), 134.23 (s), 134.27 (d), 135.11 (d), 135.36 (d), 135.73 (d), 135.76 (d), 141.53 (s), 147.82 (s). *m/z* 363. *Anal.* $C_{20}H_{17}N_3O_4$ (C, H, N).

3-Bromo-1-(2-hydroxyethoxy)methyl-2,4,5-triphenylpyrrole (***10h***), eluent A, yield 70%, was recrystallized from ethanol, m.p. 85°C. IR: 3447 (broad OH) cm^{-1}. ^1H NMR: 3.17 (2H, t, J = 4.9 Hz, CH_2), 3.39–3.43 (2H, m, CH_2), 4.72 (1H, t, J = 5.5 Hz, OH), 5.02 (2H, s, CH_2), 7.23–7.72 (15H, m, 3×C_6H_5). ^{13}C NMR (ppm): 60.04 (t), 69.60 (t), 74.58 (t), 98.22 (s), 122.89 (s), 126.66 (d), 128.12 (d), 128.19 (d), 128.51 (2d), 128.65 (d), 130.48 (d), 130.60 (s), 130.78 (d), 131.02 (s), 131.09 (d), 132.40 (s), 132.47 (s); 134.02 (s). *m/z* 447/449. *Anal.* $C_{25}H_{22}BrNO_2$ (C, H, Br, N).

1-(2-Hydroxyethoxy)methyl-3-nitro-2,4,5-triphenylpyrrole (***10i***), eluent G, yield 90%, was recrystallized from ethanol, m.p. 110°C. IR: 3588 (OH), 1499 and 1337 (NO_2) cm^{-1}. ^1H NMR (ppm): 3.05 (2H, t, J = 4.9 Hz, CH_2), 3.27–3.33 (2H, m, CH_2), 4.65 (1H, t, J = 5.5 Hz, OH), 4.92 (2H, s, CH_2), 7.04–7.65 (15H, m, 3×C_6H_5). ^{13}C NMR ($CDCl_3$, ppm): 61.41 (t), 69.29 (t), 74.00 (t), 119.54 (s), 126.98 (d), 127.79 (d), 128.40 (d), 128.44 (d), 128.64 (d), 128.90 (s), 129.60 (d), 129.78 (2s), 130.38 (d), 130.77 (d), 131.18 (d), 131.99 (s), 132.23 (s), 134.21 (s). *m/z* 414. *Anal.* $C_{25}H_{22}N_2O_4$ (C, H, N).

3-Amino-2,5-diphenyl-4-ethoxycarbonyl-1-(2-hydroxyethoxy)methylpyrrole (***10k***), eluent B, yield 75%, was obtained as an oil, b.p. 275°C. IR: 3584 (OH), 3441 and 3358 (NH_2), 1678 (CO) cm^{-1}. ^1H NMR ($CDCl_3$, ppm): 0.99 (3H, t, J = 7.1 Hz, CH_3), 3.16 (2H, t, J = 4.6 Hz, CH_2), 3.50 (2H, t, J = 4.6 Hz, CH_2), 4.06 (2H, q, J = 7.1 Hz, CH_2), 4.10 (3H, s, NH_2 and OH), 4.95 (2H, s, CH_2), 7.26–7.54 (10H, m, 2×C_6H_5). ^1H NMR (ppm): 0.90 (3H, t, J = 7.1 Hz, CH_3), 3.05 (2H, t, J = 5.5 Hz, CH_2), 3.29–3.39 (2H, m, CH_2), 3.92 (2H, q, J = 7.1 Hz, CH_2), 4.60 (1H, t, J = 5.6 Hz, OH), 4.84 (2H, s, CH_2), 6.91–7.99 (12H, m, 2×C_6H_5 and NH_2). ^{13}C NMR ($CDCl_3$, ppm): 13.80 (q), 59.19 (t), 63.34 (t), 68.68 (t), 73.76 (t), 104.30 (s), 116.46 (s), 127.12 (d), 127.59 (d), 128.34 (d), 128.96 (d), 129.48 (d), 130.98 (d), 131.84 (s), 131.96 (s), 137.60 (s), 165.54 (s). *m/z* 380. *Anal.* $C_{22}H_{24}N_2O_4$ (C, H, N).

3-Amino-4-cyano-2,5-diphenyl-1-(2-hydroxyethoxy)-methylpyrrole (***10l***), eluent C, yield 60%, was recrystallized from ethanol, m.p. 149°C. IR: 3300–3500 (broad NH_2 and OH), 2212 (CN) cm^{-1}. ^1H NMR (ppm): 3.30 (2H, t, J = 4.4 Hz, CH_2), 3.38 (3H, s, NH_2 and OH), 3.96 (2H, t, J = 4.4 Hz, CH_2), 4.94 (2H, s, CH_2), 7.51–7.64 (10H, m, 2×C_6H_5). **10l·HCl**: ^1H NMR (ppm): 3.23 (2H, t, J = 4.8 Hz, CH_2), 3.44–3.50 (2H, m, CH_2), 4.42 (3H, bs, NH_3^+), 4.78 (1H, t, J = 5.4 Hz, OH), 5.01 (2H, s, CH_2), 7.39–7.74 (10H, m, 2×C_6H_5). ^{13}C NMR (ppm): 59.98 (t), 69.53 (t), 74.51 (t), 88.82 (s), 116.38 (s), 117.95 (s), 127.37 (d), 129.10 (d), 129.23(d), 129.35(d), 129.41 (d), 129.43 (d), 130.32 (s), 130.40 (s), 133.12 (s), 139.09 (d). *m/z* 333. *Anal.* $C_{20}H_{19}N_3O_2$ (C, H, N).

5.1.4. Preparation of 2,5-diphenyl-4-ethoxycarbonyl-1-(2-hydroxyethoxy)methyl-3-nitropyrroles (***10f***)

A solution of sodium ethoxide (5 mmol) in ethanol (10 ml) was added dropwise to a solution of compound **8f** (5 mmol) in ethanol (30 ml). The reactants were stirred at room temperature until disappearance of the starting materials (TLC monitorage). 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 (eluent C) to give derivative **10f** (yield 70%), as an oil, b.p. 250°C. IR:

3503 (broad OH), 1721 (CO), 1506 and 1338 (NO_2) cm^{-1}. ^1H NMR (ppm): 1.03 (3H, t, $J=7.3$ Hz, CH_3), 3.01 (2H, t, $J=4.9$ Hz, CH_2), 3.23–3.31 (2H, m, CH_2), 4.08 (2H, q, $J=7.3$ Hz, CH_2), 4.63 (1H, t, $J=6.1$ Hz, OH), 4.92 (2H, s, CH_2), 7.49–7.64 (10H, m, $2\times C_6H_5$). ^{13}C NMR (ppm): 13.58 (q), 59.63 (t), 60.71 (t), 69.99 (t), 74.09 (t), 127.31 (s), 128.33 (s), 128.37 (d), 128.42 (s), 128.47 (d), 129.47 (d), 129.89 (d), 130.47 (d), 130.68 (d), 133.68 (s), 135.18 (s), 173.19 (s). *m/z* 410. *Anal.* $C_{22}H_{22}N_2O_6$ (C, H, N).

*5.1.5. Preparation of 3-amino-1-(2-hydroxyethoxy)methyl-2,4,5-triphenylpyrrole (**10m**)*

A solution of ammonium chloride (45 mmol) in water (5 ml) was added to a solution of **10i** (12 mmol) in ethanol (30 ml). The solution was refluxed and zinc powder (15 mmol) was added in small portions. After refluxing for a further 10 min, the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent G) to give derivative **10m** (yield 83%), m.p. 128°C. IR: 3582 (OH), 3337 and 3408 (NH_2) cm^{-1}. ^1H NMR ($CDCl_3$, ppm): 2.68 (s, broad, 3H, OH and NH_2), 3.26 (2H, t, $J=5.0$ Hz, CH_2), 3.61 (2H, t, $J=5.0$ Hz, CH_2), 5.07 (2H, s, CH_2), 7.17–7.66 (15H, m, $3\times C_6H_5$). ^{13}C NMR (ppm): 61.36 (t), 69.82 (t), 75.07 (t),116.09 (s), 119.05 (s), 126.19 (d), 126.56 (d) 127.77 (d), 128.74 (d), 128.85 (d), 129.33 (d), 129.41 (s), 129.80 (s), 130.43 (d), 131.44 (d), 132.17 (s), 132.87 (s), 133.07 (s), 135.58 (s); *m/z* 384. *Anal.* $C_{25}H_{24}N_2O_2$ (C, H, N).

*5.1.6. Preparation of 2,5-diphenyl-1-(2-hydroxyethoxy)-methylpyrrole-3-carboxylic acid (**10n**)*

Compound **8f** (2.2 mmol) was dissolved in 50% ethanol:water (20 ml) and added to a solution of potassium hydroxide (6.6 mmol) in water (20 ml). The mixture was refluxed for 4 h, cooled to room temperature and poured onto crushed ice. Upon acidification with 2 N hydrochloric acid, a yellow solid formed that was filtered, air dried and purified by column chromatography.

Elution with solvent C gave compound **10c** (yield 7%).

Further elution with solvent D gave derivative **10n** (yield 68%), which was recrystallized from ethanol, m.p. 182°C. IR: 3285 (broad OH), 1697 (CO), 1503 and 1337 (NO_2) cm^{-1}. ^1H NMR (ppm): 3.02 (2H, t, $J=4.8$ Hz, CH_2), 3.28 (2H, t, $J=4.8$ Hz, CH_2). 4.65 (1H, bs, OH), 4.91 (2H, s, CH_2), 7.46–7.90 (10H, m, $2\times C_6H_5$), 12.93 (1H, broad, OH). ^{13}C NMR (ppm): 59.88 (t), 70.16 (t), 74.25 (t), 112.29 (s), 127.69 (s), 128.55 (d),128.70 (d) 128.86 (s), 129.54 (d), 130.02 (d), 130.78 (d), 130.85 (d), 132.85 (s), 133.35 (s), 134.60 (s), 164.03 (s). *m/z* 337. *Anal.* $C_{20}H_{19}NO_4$ (C, H, N).

*5.1.7. Preparation of 3-azido-1-(2-hydroxyethoxy)methyl-2,4,5-triphenylpyrrole (**10o**)*

Hydrochloric acid (36%, 0.28 ml) was added to a suspension of the amine **10m** (10 mmol) in water (20 ml) and the mixture was diazotized with sodium nitrite (10 mmol) in water (20 ml) at room temperature. After 30 min sodium azide (20 mmol) was added in small portions and the mixture was stirred for a further 6 h at room temperature. The solid precipitate was filtered, air dried and purified by column chromatography, eluent G, to give **10o** (yield 53%), which was recrystallized from ethanol, m.p. 72°C (dec.). IR: 3500 (OH), 2106 (N_3) cm^{-1}. ^1H NMR (ppm): 3.22 (2H, t, $J=4.9$ Hz, CH_2), 3.45–3.49 (2H, m, CH_2), 4.77 (1H, t, $J=5.0$ Hz, OH), 5.00 (2H, s, CH_2), 7.26–7.73 (15H, m, $3\times C_6H_5$). ^{13}C NMR (ppm): 60.06 (t), 69.50 (t), 73.95 (t), 117.34 (s), 118.27 (s), 125.37 (s), 126.75 (d) 128.13 (d), 128.25 (2d), 128.49 (d), 128.69 (d), 129.44 (s), 130.26 (d), 130.36 (d), 130.82 (2s), 130.99 (d), 131.45 (s), 132.67 (s). *m/z* 410. *Anal.* $C_{25}H_{22}N_4O_2$ (C, H, N).

5.2. Lipophilicity measurements

The relative lipophilicity of the compounds was measured by reversed-phase thin-layer chromatography according to the method previously described [10]. R_M values were calculated from the experimental R_f values (calculated as mean values for five determinations) according to the equation $R_M=\log[(1/R_f)-1]$. Higher R_M values correspond to higher lipophilicity.

Predicted log *P* values were calculated with the Oxford Molecular software TSAR V2.22 using the atomic log *P* values determined according to Ref. [11].

5.3. Biological assays

5.3.1. Compounds

Test compounds were dissolved in DMSO at an initial concentration of 200 μM and then were serially diluted in culture medium.

5.3.2. Cells

Cell lines were from American Type Culture Collection (ATCC); bacterial and fungal strains were either clinical isolates (obtained from Clinica Dermosifilopatica, University of Cagliari) or collection strains from ATCC.

H9/III_B, MT-4 and C8166 cells (grown in RPMI 1640 containing 10% foetal calf serum (FCS), 100 UI/ml penicillin G and 100 μg/ml streptomycin were used for anti-HIV assays. Vero cells were used for anti-HSV assays.

Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco).

5.3.3. Viruses

Human immunodeficiency virus type-1 (HIV-1, III_B strain) was obtained from supernatants of persistently infected H9/III_B cells. HIV-1 stock solutions had a titre of 6×10^6 cell culture infectious dose fifty ($CCID_{50}$)/ml. Stock solutions of HSV types 1 and 2 had titres of 4 and 8×10^6 plaque forming units (PFU)/ml, respectively.

5.3.4. Anti-viral assays

Activity of compounds against the HIV-1 multiplication in acutely infected cells was based on inhibition of virus-induced cytopathogenicity in MT-4 cells. Briefly, 50 μl of RPMI 10% FCS containing 1×10^4 cells were added to each well of flat-bottomed microtiter trays containing 50 μl of medium with or without various concentrations of test compounds. 20 μl of an HIV-1 suspension containing 100 $CCID_{50}$ were added. After a 4 day incubation at 37°C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [12].

The cytotoxicity of compounds was evaluated in parallel with their anti-viral activity. It was based on the viability of mock-infected cells, as monitored by the MTT method. The activity of test compounds against HSV-1 and -2 was tested in classical plaque reduction assays [13].

5.3.5. Anti-bacterial assays

Staphylococcus aureus, group D *Streptococcus*, *Pseudomonas aeruginosa* and *Salmonella sp.* were recent clinical isolates. Tests were carried out in nutrient broth, pH 7.2, with an inoculum at 10^3 cells/tube. MICs were determined after 18 h incubation at 37°C in the presence of serial dilutions of the test compounds.

5.3.6. Anti-mycotic assays

Yeast blastospores were obtained from a 30 h old shaken culture incubated at 30°C in Sabouraud dextrose broth. The dermatophyte inoculum was scraped aseptically with a spatula from a 7 day old culture on agar and the macerate was finely suspended in Sabouraud dextrose broth using a glass homogenizer. Glycerol, final concentration 10%, was added as a cryoprotective agent to both yeast and dermatophyte suspensions, aliquots of which were then stored in liquid nitrogen. Tests tubes were inoculated with 10^3 blastospores or colony forming units (CFU)/tube. The minimal inhibitory concentration (MIC) was determined by serial dilutions using Sabouraud dextrose broth (pH 5.7) and incubating at 37°C. The growth control for yeasts was read after 1 day and for dermatophytes after 3 days (5 days for *Cryptococcus neoformans*). The MIC was defined as the compound concentration at which no macroscopic signs of fungal growth were detected. The minimal germicidal concentration (MGC) was determined by subcultivating negative test tubes in Sabouraud dextrose agar.

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