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Amphiphilic adducts of myrcene and N-substituted maleimides as potential drug delivery agents

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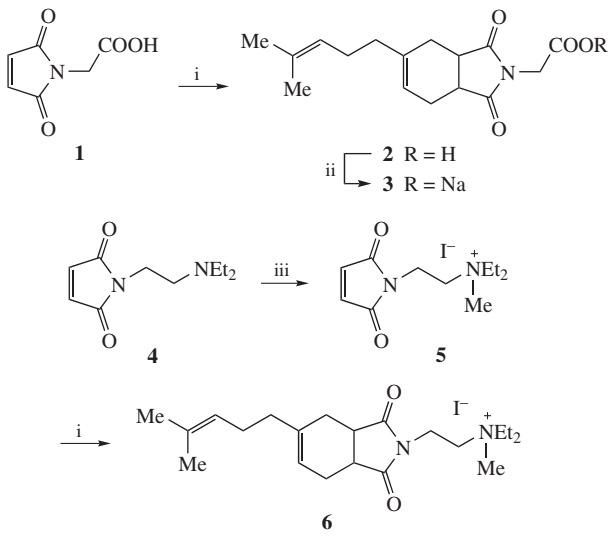
The title drug delivery compounds with pharmacophoric moieties were synthesized, and their interaction with model biomembranes (dipalmitoylphosphatidylcholine vesicles) was examined.

Targeted drug delivery is of major current interest to medicine, specifically in oncology.[1,2] The design of drugs capable of crossing cell membranes is the main problem in this field.[3] The current synthesis of pharmacologically active compounds involves the formation of hybrid molecular structures[4,5] or molecular conjugates[6–11] with different combinations of pharmacophoric functions and properties.[12,13]

Amphiphilic compounds with spatially separated hydrophilic and lipophilic fragments tend to exhibit membranotropic activity. Thus, there are great prospects in the modification of natural products, especially isoprenoids.[14–16] Furthermore, isoprenoid hydrocarbon frame structures have found application as membrane anchors in the design of modulators for membrane-integrated proteins.[17,18]

Therefore, we hypothesized that the introduction of biologically active fragments into terpenoid hydrocarbon structures may lead to their targeted delivery into subcellular compartments. To verify this hypothesis, we synthesized amphiphilic compounds containing a terpenoid hydrocarbon chain. Our aim was to determine how different hydrophilic fragments in terpenoid derivatives affect their ability to interact with a phospholipid membrane. Based on monoterpene β-myrcene, we prepared compounds containing carboxyl (**2**), carboxylate (**3**) and tertiary ammonium (**6**) groups using the Diels–Alder click reaction between N-substituted maleimides **1** and **5** and β-myrcene (Scheme 1).[†]



Scheme 1 *Reagents and conditions*: i, β-myrcene, THF, 12 h; ii, abs. THF, Na, 6 h; iii, MeCN, MeI, 20 °C.

[†] *2-[5-(4-Methylpent-3-en-1-yl)-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-isoindol-2(3*H*)-yl]acetic acid* **2**. Imide **1** (0.20 g, 1.3 mmol) was dissolved in 5 ml of THF. Then 0.34 ml (2.0 mmol) of myrcene was added to this solution. The mixture was left overnight at room temperature. Thereafter, THF was removed in a vacuum and the solid residue was recrystallized from *n*-hexane to yield 0.28 g (74%) of compound **2**, mp 84-85 °C. ^{1}H NMR ($CDCl_3$) δ: 1.59 (s, 3H, Me), 1.68 (s, 3H, Me), 2.03 (m, 4H, CH_2), 2.26 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 3.17 (ddd, 2H, CH, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 6.3 Hz, $^3J_{HH}$ 3.4 Hz), 4.25 [s, 2H, C(O)CH_2N], 5.03 (br. s, 1H, =CH), 5.57 (br. s, 1H, =CH). ^{13}C NMR ($CDCl_3$) δ: 17.7, 24.0, 25.7, 25.9, 27.5, 37.2, 39.2, 39.5, 39.8, 119.8, 123.6, 131.9, 140.2, 171.5, 179.2, 179.4. IR (ν/cm^{-1}): 1748, 1676 (C=O), 2728, 2601, 2520 (COOH). MS (MALDI-TOF), *m/z*: 291.9 $[M+H]^+$, 313.8 $[M+Na]^+$ (calc. for $[M^+]$, *m/z* 291.2). Found (%): C, 65.72; H, 7.07; N, 5.10. Calc. for $C_{16}H_{21}NO_4$ (%): C, 65.96; H, 7.27; N, 4.81.

*Sodium 2-[5-(4-methylpent-3-en-1-yl)-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-isoindol-2(3*H*)-yl]acetate* **3**. Sodium (0.1 g, 4.30 mmol) was added to the solution of compound **2** (0.10 g, 0.34 mmol) in 5 ml of abs. THF. The mixture was stirred for 6 h and then filtered. The filtrate was evaporated and solvent traces were removed in a high vacuum. Yield of compound **3** was 0.10 g (93%). ^{1}H NMR (DMSO-d_6) δ: 1.54 (s, 3H, Me), 1.62 (s, 3H, Me), 1.91 (m, 4H, CH_2), 1.98 (m, 2H, CH_2), 2.16 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 3.06 (ddd, 2H, CH, $^3J_{HH}$ 9.1 Hz, $^3J_{HH}$ 6.0 Hz, $^3J_{HH}$ 3.0 Hz), 3.56 (s, 2H, CH_2), 4.97 (br. s, 1H, =CH), 5.47 (br. s, 1H, =CH). ^{13}C NMR (DMSO-d_6) δ: 22.8, 28.7, 30.6, 30.7, 31.2, 32.2, 42.1, 43.7, 44.2, 47.7, 125.1, 129.0, 136.0, 144.6, 173.5, 184.7, 184.8. MS (MALDI-TOF), *m/z*: 313.8 $[M+H]^+$, 335.8 $[M+Na]^+$ (calc. for $[M^+]$, *m/z* 313.1). Found (%): C, 61.10; H, 6.34; N, 4.54. Calc. for $C_{16}H_{20}NNaO_4$ (%): C, 61.33; H, 6.43; N, 4.47.

*N,N-Diethyl-N-methyl-2-[5-(4-methylpent-3-en-1-yl)-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-isoindol-2(3*H*)-yl]ethanaminium iodide* **6**. Myrcene (5 ml, 29.4 mmol) was added to the solution of compound **5** (0.3 g, 0.88 mmol) in 20 ml of THF. The mixture was left at room temperature for 24 h. Thereafter, THF was removed in a vacuum and the solid residue was recrystallized from ethyl acetate to yield 0.35 g (83%) of compound **6**, mp 99–100 °C. ^{1}H NMR ($CDCl_3$) δ: 1.44 (t, 6H, Me, $^3J_{HH}$ 7.25 Hz), 1.58 (s, 3H, Me), 1.66 (s, 3H, Me), 2.00 (m, 4H, CH_2), 2.21 (m, 2H, CH_2), 2.53 (m, 2H, CH_2), 3.28 (ddd, 2H, CH, $^3J_{HH}$ 9.3 Hz, $^3J_{HH}$ 6.9 Hz, $^3J_{HH}$ 2.2 Hz), 3.32 (s, 3H, $^+$N–Me), 3.69 (m, 6H, $^+$N–CH_2), 3.89 (t, 2H, CH_2N, $^3J_{HH}$ 7.2 Hz), 5.00 (br. s, 1H, =CH), 5.53 (br. s, 1H, =CH). ^{13}C NMR ($CDCl_3$) δ: 8.5, 17.8, 23.9, 25.7, 26.1, 27.3, 32.4, 37.4, 39.6, 40.0, 48.4, 56.7, 57.7, 120.0, 123.4, 132.1, 140.5, 179.9, 180.0, 181.7. IR (ν/cm^{-1}): 1767, 1695 (C=O). MS (MALDI-TOF), *m/z*: 346.7 $[M-I]^+$ (calc. for $[M^+]$: *m/z* 474.2). Found (%): C, 52.92; H, 7.32; N, 6.09; I, 26.69. Calc. for $C_{21}H_{35}IN_2O_2$ (%): C, 53.16; H, 7.44; N, 5.90; I, 26.75.

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