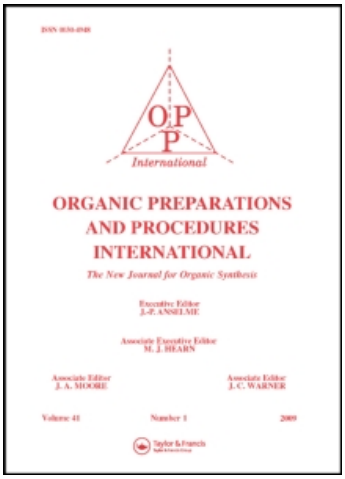


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

HEMIESTERS OF DEXANABINOL AND THEIR WATER-SOLUBLE SALTS

Emil Pop[ab]; Ferenc Soti[c]; Stanislaw Rachwal[d]
[a] Pharmos Corporation, Alachua, FL [b] Alchem Laboratories Corporation, Alachua, FL [c] Florida Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL [d] Neurogen Corporation, Branford, CT

To cite this Article Pop, Emil , Soti, Ferenc and Rachwal, Stanislaw(1999) 'HEMIESTERS OF DEXANABINOL AND THEIR WATER-SOLUBLE SALTS', Organic Preparations and Procedures International, 31: 5, 565 — 570
To link to this Article: DOI: 10.1080/00304949909355342
URL: http://dx.doi.org/10.1080/00304949909355342

HEMIESTERS OF DEXANABINOL AND THEIR WATER-SOLUBLE SALTS

Submitted by (08/03/99)

Emil Pop*[†], Ferenc Soti[††] and Stanislaw Rachwal[‡]

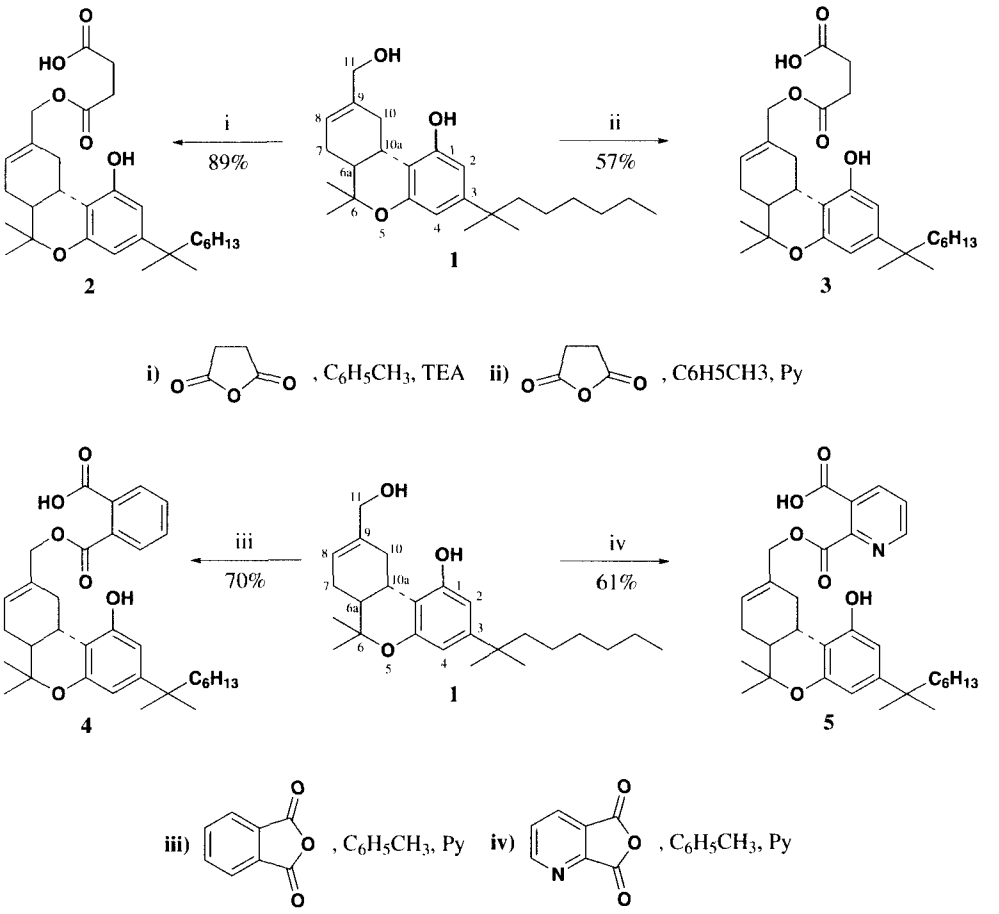
Pharmos Corporation, Alachua FL, 32615. Current Addresses:
[†] Alchem Laboratories Corporation, 13305 Rachael Boulevard, Alachua, FL 32615

[††] Florida Center for Heterocyclic Compounds, Department of Chemistry University of Florida, Gainesville FL 32611
[‡] Neurogen Corporation, 35 Northeast Industrial Road, Branford CT 06405

Unlike naturally occurring cannabinoids belonging to the (-) 6aR-*trans* series which bind to specific central and peripheral receptors,[1] the synthetic (+) 6aS-*trans* isomers have only negligible affinity to these receptors and are devoid of any psychotropic activity. The main representative of this series, [(6aS-*trans*)-6,6-dimethyl-3-(1,1-dimethylheptyl)-1-hydroxy-6a,7,10,10a- tetrahydro-6H-dibenzo[*b,d*]pyran-9-methanol] (dexanabinol, HU-211)[2] (**1**) proved to be a non-competitive N-methyl-D-aspartate (NMDA) inhibitor[3] and an effective scavenger of peroxy and hydroxy radicals;[4] accordingly it has been evaluated as a neuroprotective agent.[5-9] The further development of **1** as a therapeutic agent is somewhat hampered by its very low solubility in water, which complicates the formulation for intravenous administration. Various water-soluble esters of **1** containing polar or permanent charge-bearing moieties[10] including the glycinate salts,[11] salts of amino acid esters containing cyclic nitrogen[12] and phosphates[13] were evaluated as possible pro-drugs or congeners. The syntheses of a series of hemiesters of **1** are described herein.

Hemiesters of dicarboxylic acids, such as hemisuccinate, hemimaleate, etc, can be synthesized at one of the two or both hydroxyl functionalities present in the molecule of dexanabinol namely the C-11 allylic OH and the C-1 phenol. In this work hemiesters at the allylic OH site have been investigated. Due to differences in chemical reactivity of the two OH groups, acylation of **1** by using only a slight excess of acylating agent afforded mainly the allylic esters. Acid anhydrides (succinic, maleic, phthalic, quinolinic) were used as acylating agents, with toluene as the reaction medium. Basic catalysts (triethylamine, pyridine) were employed to increase the reaction rate (Scheme I). No 1,11-diesters were formed when succinate (**2**) maleate (**3**) and phthalate (**4**) esters were prepared. Isolation of the reaction products from the reaction mixtures was quite easy since the dicarboxylic acids (succinic, maleic, phthalic) resulting as by-products, as well as the excess of triethylamine or pyridine, were easily removed by washing the organic solution of the esters with water. The reaction of dexanabinol with the unsymmetrical quinolinic anhydride was less straightforward. Although the 2-carboxylic group of quinolinic acid is more reactive than the corresponding 3-carboxylic, the 2-pyridine carboxylate **5** of dexanabinol resulting in 60% yield, several by-products, including the 3-carboxylate, diester and phenolic esters were also formed. Column chromatography was required to isolate the pure product. Hemiesters proved to be generally more stable, and more soluble in water, in

the form of ammonium and *tris*(hydroxymethyl)aminomethane salts than as free acids. Proton-proton selective decoupling, attached proton test (APT) and 2D proton-carbon correlation (HETCOR) techniques were used to make full ^{1}H and ^{13}C NMR spectral assignments of the novel derivatives. The shift of the characteristic signal of the C-11 protons from 4.0 ppm in dexanabinol to 4.5-4.8 ppm in esters, indicate that esterification took place at the allylic OH functionality. Also, in the ^{13}C NMR spectrum of the esters only the signals of C-9, C-8 and C-11 were shifted considerably as compared to dexanabinol,[11] indicating structural modification in the allylic region.



EXPERIMENTAL SECTION

Uncorrected melting points were determined on an Electro-thermal melting point apparatus (Fisher Scientific). Elemental micro combustion analyses were performed by Atlantic Microlabs Inc., Atlanta, GA. Infrared (IR) spectra were determined on a Perkin-Elmer spectrometer in KBr pellets or liquid film. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Varian XL-300 spectrometer. Samples were dissolved in an appropriate deuterated solvent and chemical shifts were reported as parts per million (δ) relative to tetramethylsilane (0.00) which served

as an internal standard. Coupling constants (J) are reported in Hertz. High resolution mass spectrometry was performed using a Finnigan MAT95Q. The fast atom bombardment (FAB) ionization technique used: matrix: glycerol/trifluoroacetic acid. Thin layer chromatography was performed on EM reagents DC-aluminum foil plates coated to a thickness of 0.2 mm with silica gel (60 mesh). All solvents and chemicals were reagent grade. Dexanabinol was synthesized in-house.

(6aS-*trans*)-6,6-Dimethyl-3-(1,1-dimethylheptyl)-1-hydroxy-6a,7,10,10a-tetrahydro-6H-dibenzo[*b,d*]pyran-9-methanol, 11-Hydrogen Succinate (Dexanabinol Hemisuccinate) (2).- A solution of dexanabinol (0.580 g, 1.5 mmol), succinic anhydride (0.150 g, 1.5 mmol) and triethylamine (0.152 g, 1.5 mmol) in toluene (15 mL) was heated to reflux for 24 h. The solvent was evaporated *in vacuo* (temperature below 40°), traces of toluene being removed by dissolving the residue in ethyl ether (10 mL), addition of *n*-heptane (6 mL) and distillation (process repeated twice). The residue (0.820 g) which is a viscous oil was dissolved in 2% aqueous solution of tris (hydroxymethyl)aminomethane (50 mL) by stirring 2 h, and poured into a cold (0-5°) 2% aqueous solution of HCl with stirring. The solid which settled was collected, rinsed with water (5 x 100 mL) and dried over P_2O_5 to give 0.650 g (yield 89%) of **2**, as a hygroscopic off-white solid, mp 58-62°, Purity (HPLC) 97%.

IR (KBr pellet) cm^{-1}: 3424 and 3226 (2x ν OH), 2961 (ν_{as} CH_3), 2826 (ν_{as} CH_2), 2894 (ν_s CH_3), 2868 (ν_s C=O), 1736 (ν_s C=O), 1719 (ν_s C=O), 1625 (ν C=C olefin), 1578 (phenyl nucleus), 1459 (δ_s CH3), 1415, 1384 and 1371 (gem. dimethyl), 1267 (ν_s C-O-C), 1186 (ν_s C-O-C), 1085 (ν C-C phenol), 968 (γCH, Ar), 839 (γCH, olefin).

UV (methanol): 276 nm (log ε: 3.09), 282 nm (log ε: 3.10).

^1H NMR: 0.84 (t, J = 6.5 Hz, 3 H), 1.07 (m, 2 H), 1.11 (s, 3 H), 1.15-1.30 (m, 6 H), 1.20 (s, 6 H), 1.38 (s, 3 H), 1.48 (m, 2 H), 1.82 (m, 3 H), 2.21 (m, 1 H), 2.62 (s, 4 H), 2.67 (m, 1 H), 3.45 (dd, J = 3.78, 16.87 Hz, 1 H), 4.56 (d, J = 11.9Hz, 1 H), 4.75 (d, J = 11.9, 1 H), 5.77 (d, J = 4.4 Hz, 1 H), 6.29 (d, J = 1.65 Hz, 1 H), 6.34 (d, J = 1.8 Hz, 1 H).

^{13}C NMR δ: 13.8, 18.2, 22.4, 24.4, 27.3, 27.5, 28.5 (2 C), 28.9 (2 C), 29.1, 29.8, 31.0, 31.6, 37.0, 44.4, 44.6, 68.3, 75.9, 105.4, 106.5, 109.5, 124.1, 133.6, 149.5, 153.9, 155.6, 172.1, 174.1. MS(FAB) $[M + H]^+$ (m.z.): 487 for $C_{29}H_{41}O_6$. (M.W. 485.62).

tris(Hydroxymethyl)aminomethane Salt of Dexanabinol Hemisuccinate (2a).- To a 2% aqueous solution of tris(hydroxymethyl)aminomethane (20 mL) placed in a 25 mL glass vial (Wheaton), **2** (600 mg) was added. The vial was closed and sonicated for 40-60 mm until a homogenous micellar solution was formed, then polyvinyl pyrrolidone (PVP K-15) (400 mg) and D(-)-mannitol (400 mg) was added and the mixture sonicated until solution. Osmolarity of the solution was adjusted to 280-320 mOsmol/Kg by mannitol addition. The solution was filtered through a sterile 0.2 μM PTFE filter membrane (25 mm diameter) and then freeze-dried. By reconstitution, an injectable solution of 20 mg/mL of **2a** can be obtained.

(6aS-*trans*)-6,6-Dimethyl-3-(1,1-dimethylheptyl)-1-hydroxy-6a,7,10,10a-tetrahydro-6H-dibenzo[*b,d*]pyran-9-methanol, 11-Hydrogen Maleate (Dexanabinol Hemimaleate) (3).- A solu-

tion of **1** (100 mg, 0.26 mmol), maleic anhydride (29.4 mg, 0.30 mmol) and pyridine (24.3 µL, 0.30 mmol) in toluene (1 mL) was stirred under argon at 20~25° for 24 h. The solution was poured into ice-water (20 g), acidified with acetic acid to pH 5 and extracted with toluene: ethyl acetate (20 mL, 1:1), The organic solution was washed with ice cold water (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure (temperature below 40°). The residue was purified by column chromatography (silica gel, eluent toluene: ethyl acetate: dioxane: ethanol, 1:1:1:1). Pure **3** (71.8 mg, 57% yield) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 6.4 Hz, 3 H), 1.08 (m, 2 H), 1.10 (s, 3 H), 1.00-1.30 (m, 6 H), 1.18 (s, 6 H), 1.39 (s, 3 H), 1.47 (m, 2 H), 1.87 (m, 3 H), 2.25 (m, 1 H), 2.70 (m, 1 H), 3.40 (dd, J = 2.7,14.9 Hz, 1 H),4.57 (d, J = 11.9Hz, 1 H), 4.73 (d, J = 11.9, 1 H), 5.86 (d, J = 4.01, 1 H), 6.29 (d, J = 1.5 Hz, 1 H), 6.32 (m, 1 H), 6.37 (m, 1 H), 6.38 (d, J = 1.7 Hz, 1 H), 8.05 (bs, 2H). ^{13}C NMR: δ 14.1, 18.4, 22.6, 24.6, 27.5, 27.7, 28.7 (2 C), 30.0, 31.3, 31.7, 31.8, 37.3, 44.4, 44.6, 70.5, 76.3, 105.7, 107.7, 109.4, 126.8, 128.4, 132.6, 133.9, 150.3, 154.2, 154.6, 166.6, 166.9.

Dexanabinol Ammonium Hemimaleate (3a).- A mixture of **1** (103.7 mg, 0.2 mmol), maleic anhydride (132.1 mg, 1.35 mmol) pyridine (1.62 µL, 2.0 mmol) in toluene (2.0 mL) was stirred under argon at 25° for 6 h. Aqueous 5% $NaHCO_3$ (6 mL, 3.57 mmol was added to the mixture and the stirring was continued for 30 min. The reaction mixture was extracted with ether (30 mL) then the organic solution was washed with 5% aqueous $NaHCO_3$ (5 mL), water (10 mL), diluted (pH 3) H_2SO_4 (3 mL) and water (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was dissolved in ether (92 mL) and the solution was saturated with gaseous ammonia. The solvent and excess ammonia were evaporated. The residue was triturated with hexane and dried to give **3a** as a yellow powder (87.6 mg, 65% yield), mp. 90-100°.

Anal. Calcd for $C_{29}H_{43}NO_6$: C, 69.43; H, 8.64; N, 2.79. Found: C, 69.16; H, 8.54; N, 2.54

(6aS-*trans*)-6,6-Dimethyl-3-(1,1-dimethylheptyl)-1-hydroxy-6a,7,10,10a-tetrahydro-6H-dibenzo[*b,d*]pyran-9-methanol, 11-Hydrogen Phthalate (Dexanabinol Hemiphthalate) (4).- A mixture of **1**(196.6 mg, 0.51 mmol), phthalic anhydride (110.9 mg, 0.75 mmol), pyridine (81 µL, 1.00 mmol) and toluene (2.0 mL) was stirred under argon at 25° for 24 h. Aqueous 5% $NaHCO_3$ (6 mL, 3.57 mmol) was added and the resulting mixture was stirred for an additional 30 mm. Acetic acid was then added dropwise to reduce the pH of the mixture from 8.0 to 7.0. Water (20 mL) was added and the reaction mixture was extracted with ether (20 mL). The organic layer was washed with water (20 mL), 10% aqueous acetic acid (70 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue dissolved in toluene (20 mL) and evaporated to completely remove the acetic acid. The solid residue was dried to give pure **4** (191.9 mg, 70%) as a white powder, mp. 88-89°. ^{1}H NMR ($CDCl_3$): δ 0.83 (t, J = 6.7 Hz, 3 H), 1.02 (m, 2 H), 1.08 (s, 6 H), 1.09 (s, 3 H), 1.13 (m, 2 H), 1.18 (m, 2 H), 1.22 (m, 2 H), 1.37 (s, 3 H), 1.41 (m, 2 H), 1.84 (m, 1 H), 1.87 (m, 1 H), 1.95 (m, 1 H), 2.25 (m, 1 H), 2.70 (td, J = 10.5 Hz, 4.4 Hz, 1 H), 3.48 (dd, J =4.1, 1 H), 4.57 (d, J = 11.4 Hz, 1 H), 4.95 (d, J = 11.5 Hz, 1 H), 5.92 (d, J =4.1 Hz, 1 H), 6.22 (d, J = 1.7 Hz, 1 H), 6.35 (d, J = 1.7 Hz, 1 H), 7.38 (bs, 1 H), 7.57 (m, 2 H), 7.72 (m, 1 H), 7.86 (m, 1 H). ^{13}C NMR :δ 14.1, 18.4, 22.7, 24.6, 27.5, 27.9, 28.5 (2 C), 30.0, 31.2, 31.8, 32.0, 37.2, 44.4, 44.6, 70.6, 76.4, 105.6, 107.8, 109.5, 127.1, 128.9, 129.9, 130.0,

130.9, 132.1, 133.1, 133.2, 150.2, 154.2, 154.4, 168.7, 171.4.

Anal. Calcd for $C_{33}H_{42}O_6$: C, 74.13; H, 7.92. Found: C, 73.91; H, 8.08

Dexanabinol Ammonium Hemiphthalate (4a).- A solution of **4** (60 mg, 0.11 mmol) in ether (2 mL) was saturated with gaseous ammonia and the solvent and excess ammonia were evaporated. The solid residue was triturated with hexanes: ether 1:1(2 mL), filtered and dried in vacuum (50°) to give pure **4a** (47.7 mg, 79% yield) as colorless prisms, mp. 118-121°.

Anal. Calcd for $C_{33}H_{45}NO_6$: C, 71.84; H, 8.22; N, 2.54. Found: C, 71.67; H, 8.11; N, 2.31

(6aS-*trans*)-6,6-Dimethyl-3-(1,1-dimethylheptyl)-1-hydroxy-6a,7,10,10a-tetrahydro-6H-dibenzo[*b,d*]pyran-9-methanol, 11-(3-Carboxy-2-pyridine) Carboxylate (Dexanabinol Hemiquinolinate) (5).- A mixture of **1** (208.8 mg, 0.54 mmol) 2,3-pyridinecarboxylic anhydride (198.1 mg, 1.33 mmol), pyridine (81 µL, 1.0 mmol) in toluene (2,0 mL) was stirred under argon at 25° for 24 h. The reaction mixture was poured into ice-water (25 g) and extracted with ether (30 mL). The organic layer was washed with water (20 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica gel, eluent, ethyl acetate: ethanol: TEA, 7:2:1). The fractions containing the main reaction product were evaporated, the residue dissolved in ether (30 mL), the solution washed with pH 3 aqueous H_2SO_4 (2 x 20 mL), water (20 mL), and dried ($MgSO_4$). After evaporation of the solvent and drying, **5** was obtained (176.3 mg, 61%) as a white solid, mp. 150-153° (dec.).

^{1}H NMR ($CDCl_3$): δ 0.83 (t, J = 6.7 Hz, 3 H), 1.02 (m, 2 H), 1.05 (s, 3 H), 1.11 (s, 3 H), 1.17 (m, 6 H), 1.35 (s, 3 H), 1.43 (m, 2 H), 1.83 (m, 2 H), 1.88 (m, 1 H), 2.21 (m, 1 H), 2.66 (td, J =10.6 Hz, 1 H), 3.50 (dd, J = 17.1 Hz, 1 H), 4.75 (d, 11.5 Hz, 1 H), 4.87 (d, J = 11.6 Hz, 1 H), 5.91 (d, J = 4.2 Hz, 1 H), 6.24 (d, J = 1.7 Hz, 1 H), 6.33 (d, J = 1.7 Hz, 1 H), 7.46 (dd, J = 4.9, 7.9 Hz, 1 H), 7.47 (bs, 1 H), 8.26 (dd, J = 1.5, 1 H), 8.78 (dd, J = 1.5, 1 H, 4.9 Hz).

^{13}C NMR: δ 14.1, 18.3, 22.7, 24.6, 27.5, 27.8, 28.5, 28.7, 30.0, 31.2, 31.7, 31.8, 37.2, 44.4, 44.6, 70.7, 76.3, 105.7, 107.6, 109.6, 124.9, 126.5, 126.9, 132.8, 138.6, 150.1, 151.6, 154.2, 154.7, 166.9, 168.5.

Anal. Calcd for $C_{32}H_{41}NO_6$: C, 71.75; H, 7.71; N, 2.61. Found: C, 71.56; H, 7.86; N, 2.66

Dexanabinol Ammonium Hemiquinolinate (5a).- A solution of **5** (13.5 mg, 0.025 mmol) in ether (1 mL) was saturated with ammonia (gas). The solvent and excess of ammonia were evaporated and the solid residue was triturated with hexanes (1 mL). The solid was dried to give **5a** (7.1 mg, 51%) as a white solid.

Anal. Calcd for $C_{32}H_{44}N_2O_6$: C, 69.54; H, 8.02; N, 5.07. Found: C, 69.65; H, 8.12; N, 4.87

REFERENCES

1. W. A. Devane, F. A. Dysarz III, M. R. Johnson, L. S. Melvin, and A. C. Howlett, *Mol. Pharmacol.*, **34,** 605 (1988).

2. R. Mechoulam, N. Lander, A. Breuer and J. Zahalka, *Tetrahedron: Asymmetry*, **1**, 315 (1990).

3. J. J. Feigenbaum, F. Bergmann, S. A. Richmond, R. Mechoulam, V. Nadler, Y. Kloog and M. Sokolovsky, *Proc. Natl. Acad. Sci. U.S.A.*, **86**, 9584 (1989).

4. N. Eshhar, S. Striem, R. Kohen, O. Tirosh and A. Biegon, *Eur. J. Pharmacol.*, **283,** 19-29 (1995).

5. N. Eshhar, S. Striem and A. Biegon, *Neuro. Report*, **5**, 237 (1993).

6. E. Shohami, M. Novikov, and R. Mechoulam, *J. Neurotrauma,* **10**, 109 (1993).

7. A. Bar-Joseph, Y. Berkovitch, J. Adamchik and A. Biegon, *Molecular and Chemical Neuropathology*, **23**, 125 (1994).

8. E. Shohami, M. Novikov and R. Bass, *Brain Res.*, **674**, 55 (1995).

9. M. E. Brewster, E. Pop, R. L. Foltz , S. Reuschel, W. Griffith, S. Amselem and A. Biegon, *Int J Clin Pharmacol,* **35**, 361 (1997).

10. E. Pop, M. E. Brewster, Z. Z. Liu, F. Soti, S. Rachwal, A. Dinculescu, V. Nadler, Y. Barenholz, R. Mechoulam and A. Biegon, *Proceedings of the 1-St. World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology,* (APGI-APV) Budapest, pp. 127-128 (1995).

11. E. Pop, Z. Z. Liu, M. E. Brewster, Y. Barenholz, V. Korablyov, R. Mechoulam, V. Nadler and A. Biegon, *Pharm. Res.*, **13**, 62 (1996).

12. E. Pop, F. Soti, M. E. Brewster, Y. Barenholz, V. Korablyov, R. Mechoulam, V. Nadler and A. Biegon, *ibid.*, **13,** 469 (1996)

13. E. Pop, F. Soti, A. Biegon and M. E. Brewster, *Org. Prep. Proced. Int.*, **29**, 341 (1997)

****