**Tandem Achmatowicz-Knoevenagel protocol: Diastereoselective synthesis and anticancer evaluation of cyclopenta[b]pyrane derivatives**

Taleb H. Al-Tel, *† M. H. Semreen† and Wolfgang Voelter§

†College of Pharmacy, University of Sharjah, P.O.Box 27272, Sharjah, UAE, and Sharjah Institute for Medical Research-Cancer Division, 27272, Sharjah, UAE, § Interfakultäres Institut für Biochemie, Eberhard-Karls-Universität Tuebingen, Hoppe-Seyler-Straße, 72076, Tuebingen-Germany.

Tel.: +971 501732950; fax: +971 6 5585812; E-mail: taltal@sharjah.ac.ae,

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**Experimental Section**

All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven dried or flamed graduated vessels. Solvents were dried and purified by conventional methods prior use. Flash column chromatography was performed with Silica gel 60, 0.040-0.063 mm (230-400 mesh). Aluminium backed plates pre-coated with silica gel 60 (UV254) were used for thin layer chromatography. $^1$H, $^{13}$C spectra were recorded on 250 MHz / 63 MHz or 400/ 100.7 MHz spectrometers. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, CHCl$_3$ (7.27 ppm, 1H; 77.16 ppm, the middle peak, $^{13}$C). Elemental analysis was performed on elemental analyzer. The FD mass spectra were recorded using a mass spectrometer connected to a PDO 11/34 (DEC) computer system. All compounds were determined to be >95% pure by high-performance liquid chromatography (HPLC). Purity of compounds
were determined on a Phenomenex Luna C18- (2), 3 mm column, 4.6 mm i.d. × 30 mm length, with 30-75% acetonitrile/water/0.1% trifluoroacetic acid, 1.0 mL/min elution at rt using 210, 254, or 280 nm wavelength.

**General procedure of the synthesis of compounds 5a and 5b.** A suspension of NaH (174 mg, 4.4 mmol, 65% dispersion in mineral oil) in 10 mL of THF at 0 °C was cautiously treated with tert-butyl acetoacetate (0.66 mL, 4 mmol) under argon over a 15 min period. After stirring at this temperature for 30 min, a solution of n-BuLi (2.75 mL, 4.4 mmol, 1.6 M in n-hexane) was added dropwise over 10 min. The mixture was stirred at 0 °C for 30 min. The resultant milky solution was cooled to -78 °C then 4 mmoles of either furfural (384 mg) or 2-acetylfuran (440 mg) in 10 ml of THF was added. The reaction was then stirred at the same temperature for 1 h, after which the mixture was quenched with a saturated solution of NH₄Cl (15 mL), extracted with EtOAc (3 × 30 mL), dried over Na₂SO₄ and concentrated under vacuum to give a yellowish crude oil. The crude was purified through a short silica gel column using hexane/ EtOAc (9:1) as eluent to afford compounds 5a (917 mg, 95% yield) and 5b (977 mg, 91% yield) as a yellowish oils.

**tert-Butyl 5-(2-furyl)-5-hydroxy-3-oxopentanoate (5a).** 
\( ^1H \) NMR (250 MHz, CDCl₃) \( \delta \) 7.31 (dd, \( J = 0.8, 1.8 \) Hz, 1H, H-5'), 6.30 (dd, \( J = 3.2 \) Hz, 1H, H-4'), 6.22 (d, \( J = 3.2 \) Hz, 1H, H-3'), 5.13 (dd, \( J = 3.3, 8.3 \) Hz, 1H, H-5), 3.37 (s, 2H, H-2a, H-2b), 3.10 (dd, \( J = 3.3, 17.5 \) Hz, 1H, H-4a), 1.39 (CO₂C(CH₃)₃); \(^{13}C\) NMR (63 MHz, CDCl₃) \( \delta \) 202.7 (C-2), 166.1 (CO₂C(CH₃)₃), 154.8 (C-2'), 110.3 (C-5'), 110.2 (C-4'), 106.3 (C-3'), 82.3 (CO₂C(CH₃)₃), 63.5 (C-5), 51.1 (C-2), 47.8 (C-4), 27.9 (CO₂C(CH₃)₃); FD-MS m/z = 255 (M + 1)<sup>+</sup>, Anal. Caled for C₁₃H₁₈O₅ (254.28); C, 61.40; H, 7.14. Found: C, 61.20; H, 7.31.

**tert-Butyl 5-(2-furyl)-5-hydroxy-3-oxohexanoate (5b).** 
\( ^1H \) NMR (250 MHz, CDCl₃) \( \delta \) 7.22 (dd, \( J = 0.9, 1.8 \) Hz, 1H, H-5'), 6.02 (dd, \( J = 1.8, 3.2 \) Hz, 1H, H-4'), 6.15 (dd, \( J = 0.9, 3.3 \) Hz, 1H, H-3'), 3.25 (bs, 2H, H-2a, H-2b ), 3.18 (d, \( J = 16.5 \) Hz, 1H, H-4a), 2.82 (d, \( J = 16.5 \) Hz, 1H, H-4b), 1.43 (CH₃), 1.63 (CO₂C(CH₃)₃); \(^{13}C\) NMR (63 MHz, CDCl₃) \( \delta \) 203.0 (C-3), 165.0 (CO₂C(CH₃)₃), 158.5 (C-2'), 110.3 (C-5'), 106.3 (C-4'), 82.3 (CO₂C(CH₃)₃), 63.5 (C-5), 51.1 (C-2), 47.8 (C-4), 27.9 (CO₂C(CH₃)₃); FD-MS m/z = 255 (M + 1)<sup>+</sup>, Anal. Caled for C₁₃H₁₈O₅ (254.28); C, 61.40; H, 7.14. Found: C, 61.20; H, 7.31.
110.2 (C-4'), 104.7 (C = 3'), 82.0 (CO₂C(CH₃)₃), 70.0 (C-5), 51.7 (C-2), 51.5 (C-4), 28.2 (CO₂C(CH₃)₃), 27.6 (CH₃); FD-MS m/z = 269 (M + 1)⁺, Anal. Calcd for C₁₄H₂₀O₅ (268.31); C, 62.67; H, 7.51. Found: C, 62.51; H, 7.42.

**General procedure for the synthesis of compounds 7a and 7b.** A solution of 5a (1270 mg, 5 mmol) or 5b (1341.5 mg, 5 mmol) in dichloromethane (40 mL) at 0 °C was treated with m-chloroperbenzoic acid (1376 mg, 8.0 mmol of 80% aqueous slurry) which was dissolved in 30 ml DCM, dried over Na₂SO₄, filtered, diluted with 50 ml toluene and dried under reduced pressure) and stirred at 0 °C for 6 h. Sodium sulfite solution (30 mL of 10%) was introduced, and the layers were separated after 1 h of rapid mixing. The aqueous phase was washed with saturated sodium bicarbonate solution (30 mL), brine and water (30 mL) prior to drying and solvent evaporation. The crude viscous yellowish oils (6a and 6b) was used in the next step without further purification.

A solution of the crude anomeric mixture of 6a (852 mg, 3 mmol) or 6b (810 mg, 3 mmol) in dry toluene (30 ml), freshly prepared piperidinium acetate (3.9 mmol) and 4 °A molecular sieves (250 mg) was stirred at 50 °C for 4 h. The hot mixture was filtered and evaporated under reduced pressure. The brown viscous oil was dissolved in EtOAc and extracted with saturated solution of NaHCO₃, brine, water and dried over Na₂SO₄. The crude was purified on a silica gel column using hexane/ EtOAc (7:3) as eluent to afford compounds 7a (350 mg, 68% yield) and 7b (425 mg, 73% yield) as amorphous solids.

**tert-Butyl (7aS)-2-hydroxy-6-oxo-2,6,7,7a-tetrahydrocyclopenta[b]pyran-5-carboxylate (7a).** ¹H NMR (250 MHz, CDCl₃) δ 7.25 (bt, J = 10.1 Hz, 1H, H-3), 6.42 (dd, J = 3.3, 10.1 Hz, 1H, H-4), 5.60 (bs, 1H, H-2), 5.16 (dd, J = 4.7, 6.8 Hz, 1H, H-7a), 2.84 (dd, J = 6.8, 17.6 Hz, 1H, H-7), 2.51 (dd, J = 4.6, 17.6 Hz, 1H, H-7'), 15.3 (s, 9H, 1BuO); ¹³C NMR (63 MHz, CDCl₃) δ 199.1, 199.2 (C-6), 170.5, 170.7 (C-4a), 166.2 (CO₂C(CH₃)₃), 142, 138.2 (C-3), 125.0, 123.0 (C-4), 92.7, 89.1 (C-2), 82.0, 71.5 (CO₂C(CH₃)₃), 65.5 (C-7a), 42.5, 42.3 (C-7), 28.2 (CO₂C(CH₃)₃); FD-MS m/z = 252 (M)+, Anal. Calcd for C₁₃H₁₆O₅ (252.10); C, 61.90; H, 6.39. Found: C, 61.85; H, 6.43.
**tert-Butyl (7aS)-2-hydroxy-7a-methyl-6-oxo-2,6,7,7a-tetrahydrocyclopenta[b]pyran-5-carboxylate (7b).** $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.13 (m, 2H, H-3), 6.32 (m, 2H, H-4), 5.59, 5.51 (bs, 2H, H-2), 2.57 (m, 4H, H-7,7'), 1.42 (bs, 12H, CH$_3$-7a, CO$_2$C(CH$_3$)$_3$); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 198.8, 198.5 (C-6), 170.5, 170.4 (C-4a), 161.1 (CO$_2$C(CH$_3$)$_3$), 141.5, 138.5 (C-3), 125.7, 125.3 (C-5), 122.5, 121.3 (C-4), 89.6, 88.7 (C-2), 82.5 (CO$_2$C(CH$_3$)$_3$), 77.5, 73.9 (C-7a) 52.2, 51.9 (C-7), 28.9, 24.2 (CH$_3$ = 7a), 28.1, 27.8 (CO$_2$C(CH$_3$)$_3$); FD-MS m/z = 266 (M)+, Anal. Calcd for C$_{13}$H$_{16}$O$_5$ (266.12); C, 63.15; H, 6.81. Found: C, 63.09; H, 6.87.

**General procedure for the synthesis of compounds 8a, 8b and 9.** A solution of the anomeric mixture of 7a (756 mg, 3 mmol) or 7b (798 mg, 3 mmol) in MeI (15 mL) at rt was treated with 3.0 mmol of Ag$_2$O. The progress of reaction was monitored by TLC (12 h). When complete, the reaction mixture was filtered over celite. The filtrate was washed with saturated solutions of sodium sulfite, sodium bicarbonate, brine, dried and evaporated. The residue was purified on silica gel column using hexane/EtOAc (9:1) as an eluent.

**tert-Butyl (2S,7aS)-2-methoxy-6-oxo-2,6,7,7a-tetrahydrocyclopenta[b]pyran-5-carboxylate (8a).** Yiel: 540 mg, 80%; Significant NMR NOEs are 2-H to 7a-H, 36%; 7a-H to 2-H, 32%. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.20 (dd, $J = 0.4$, 10.1 Hz, 1H, H-3), 6.30 (dd, $J = 3.3$, 10.1 Hz, 1H, H-4), 5.00 (dd, $J = 3.3$ Hz, 1H, H-2), 4.96 (dd, $J = 4.8$, 6.9 Hz, 1H, H-7a), 3.45 (s, 3H, OMe), 2.80 (dd, $J = 4.5$, 17.6 Hz, 1H, H-7'), 1.48 (s, 9H, CH$_3$-7a), 1.47 (s, 3H, OMe); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 197.8 (C-6), 166.1 (C-4a), 160.8 (CO$_2$C(CH$_3$)$_3$), 137.2 (C-3), 123.0 (C-4), 127.0 (C-5), 95.6 (C-2), 82.5 (CO$_2$C(CH$_3$)$_3$), 65.5 (C-7a), 56.4 (OMe), 42.3 (C-7), 28.0 (CO$_2$C(CH$_3$)$_3$); FD-MS m/z = 266 (M)+, Anal. Calcd for C$_{14}$H$_{18}$O$_5$ (266.16); C 63.12, H 6.82. Found: C 63.51, H 6.55.

**tert-Butyl (2S,7aS)-2-methoxy-7a-methyl-6-oxo-2,6,7,7a-tetrahydrocyclopenta[b]pyran-5-carboxylate (8b).** Yiel: 742 mg, 94%; Significant NMR NOEs are 2-H to 7a-CH$_3$, 31%; 7a-CH$_3$ to 2-H, 33%. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.26 (dd, $J = 1.7$, 10.0 Hz, 1H, H-3), 6.62 (dd, $J = 1.6$, 10.0 Hz, 1H, H-4), 5.10 (bd, $J = 3.1$ Hz, 1H, H-2), 3.44 (s, 3H, OMe), 2.74 (d, $J = 17.1$ Hz, 1H, H-7), 2.57 (d, $J = 17.1$ Hz, 1H, H-7'), 1.48 (s, 3H, 7a-CH$_3$), 1.47 (s, 9H, CO$_2$C(CH$_3$)$_3$); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 197.7 (C-6), 169.4 (C-4a), 160.9
tert-Butyl (2R,7aS)-2-methoxy-6-oxo-2,6,7,7a-tetrahydrocyclopenta[b]pyran-5-carboxylate (9). Yield: 138 mg, 20%; Significant NMR NOEs are 2-OMe to 7a-H, 37%; 7a-H to 2-OMe, 29%. 1H NMR (250 MHz, CDCl3) δ 7.25 (dd, J = 2.1, 10.1 Hz, 1H, H-3), 6.32 (dd, J = 1.4, 10.1 Hz, 1H, H-4), 5.34 (dd, J = 0.6, 2.0 Hz, 1H, H-2), 4.74 (dd, J = 4.7, 6.9 Hz, 1H, H-7a), 3.47 (s, 3H, OMe), 3.30 (dd, J = 6.8, 17.7 Hz, 1H, H-7), 2.55 (dd, J = 4.6, 17.7 Hz, 1H, H-7'), 1.47 (s, 9H, (CO2C(CH3)3); 13C NMR (63 MHz, CDCl3) δ 171.5 (CO2C(CH3)3), 169.7 (C-4a), 141.6 (C-3), 124.8 (C-4), 98.7 (C-2), 82.0 (CO2C(CH3)3), 71.4 (C-7a), 56.0 (OMe), 42.6 (C-7), 28.2 (CO2C(CH3)3); FD-MS m/z = 266 (M)+, Anal. Calcd for C14H18O5 (266.12); C 63.15, H 6.81; Found: C 62.98, H 7.11.

tert-Butyl (2S,4aS,5R,7aS)-2-methoxy-7a-methyl-6-oxoctahydrocyclopenta[b]pyran-5-carboxylate (10). To a stirred solution of 8b (560 mg, 2.0 mmol) in dry EtOAc/MeOH (1:1, 20 mL) was added Pd/C (56 mg, 15% Pd/C w/w). The mixture was placed under 1.0 atm of H2 pressure, and the progress of reaction was monitored by TLC. After 2 h, the solid was removed by filtration through a celite pad, which was washed repeatedly with EtOAc. After concentration of the filtrate, the residue was purified on silica gel column (elution with 5% ethyl acetate in hexane) to give 10 as amorphous solid (430 mg, 87%). Significant NMR NOEs are 4a-H to 5-H, 37%; 7a-CH3 to 2-H, 31%; 7a-CH3 to 2-H, 35%; 4aH to 2-OMe, 21%. 1H NMR (250 MHz, CDCl3) δ 4.73 (dd, J = 2.4, 9.8 Hz, 1H, H-2), 3.29 (d, J = 6.2 Hz, 1H, H-5), 3.24 (s, 3H, OMe), 2.79 (d, J = 18.4 Hz, 1H, H-7), 2.45 (ddd, J = 2.3, 4.6, 6.2 Hz, 1H, H-4a), 2.31 (d, J = 18.4 Hz, 1H, H-7'), 1.97 (m, 2H), 1.74 (dm, J = 17.0 Hz, 1H) 1.65 (dm, J = 13.0 Hz, 1H), 1.49 (s, 3H, CH3-7a), 1.41 (s, 9H, CO2C(CH3)3); 13C NMR (63 MHz, CDCl3) δ 210.3 (C-6), 171.0 (CO2C(CH3)3), 95.7 (C-2), 82.2 (CO2C(CH3)3), 81.7 (C-7a), 60.2 (C-5), 56.8 (OMe), 55.0 (C-7), 51.5 (C-4a), 34.0 (C-3), 28.4(CO2C(CH3)3), 25.4 (C-4), 24.7 (CH3-7a); FD-MS m/z = 284 (M)+, Anal. Calcd for C15H20O5 (284.35); C 63.40, H 8.51; Found: C 63.52, H 8.46.
General procedure for the synthesis of compounds 11a-f. The bicyclic β-ketoester 10 derived from the reduction product of 8b (142 mg, 0.5 mmol) and the desired hydrazine derivative (0.52 mmol) in 20 ml absolute ethanol was refluxed, and the progress of reaction was monitored by TLC. After 6 h, the reaction mixture was concentrated on a rotary evaporator, the residue was purified on silica gel column (elution with 10% ethyl acetate in hexane) to give 11a-f as amorphous solids.

(3bS,6S,7aS)-6-Methoxy-7a-methyl-2-(4-methylphenyl)-1,2,3b,4,5,6,7a,8-octahydro-3H-pyrano[3',2':3,4]cyclopenta[1,2-c]pyrazol-3-one (11a). Yield: 122 mg, 88%; 1H NMR (400 Mz, CDCl3) δ 7.70 (d, J = 7.3 Hz, 2H, Ar-H), 7.17 (d, J = 7.3 Hz, 2H, Ar-H), 4.64 (dd, J = 2.7, 7.9 Hz, 1H, H-2), 3.04 (bd, J = 6.2 Hz; 1H), 3.30 (s, 3H, OMe), 2.25 (dd, J = 4.6, 11.3 Hz, 1H), 2.20 (m, 3H), 2.17 (s, 3H, Ar-CH3), 1.90 (m, 3H), 1.45 (s, 3H, CH3-7a); 13C NMR (100.7 MHz, CDCl3) δ 159.6, 143.0, 141.7, 137.4, 133.4, 132.6, 125.9, 115.6, 94.2, 84.1, 60.2, 56.8, 55.0, 34.1, 25.4, 24.7, 20.9; FD-MS m/z = 314 (M)+, Anal. Calcd for C18H22N2O3 (314.38); C, 68.77; H, 7.05; N, 8.91. Found: C, 68.56; H, 7.24; N, 9.07.

4-[(3bS,6S,7aS)-6-Methoxy-7a-methyl-3-oxo-1,3,3b,4,5,6,7a,8-octahydro-2H-pyranono[3',2':3,4]cyclopenta[1,2-c]pyrazol-2-yl]benzonitrile (11b). Yield: 91.5 mg, 75% 1H NMR (400 Mz, CDCl3) δ 7.81 (dd, J = 1.2, 7.4 Hz, 2H, Ar-H), 7.73 (dd, J = 1.1, 7.4 Hz, 2H, Ar-H), 4.90 (dd, J = 3.1, 8.2 Hz, 1H, H-2), 3.01 (bd, J = 6.4 Hz; 1H), 3.41 (s, 3H, OMe), 2.62 (m, 2H), 2.46 (dd, J = 4.3, 10.1 Hz, 1H), 2.23 (m, 2H), 1.92 (m, 2H), 1.49 (s, 3H, CH3-7a); FD-MS m/z = 325 (M)+, Anal. Calcd for C18H19N3O3 (325.14); C, 66.45; H, 5.89; N, 12.91. Found: C, 66.27; H, 5.95; N, 12.70.

(3bS,6S,7aS)-6-Methoxy-7a-methyl-2-(4-nitrophenyl)-1,2,3b,4,5,6,7a,8-octahydro-3H-pyrano[3',2':3,4]cyclopenta[1,2-c]pyrazol-3-one (11c). Yield: 104 mg, 78%; 1H NMR (400 Mz, CDCl3) δ 8.34 (dd, J = 0.9, 6.9 Hz, 2H, Ar-H), 8.18 (dd, J = 1.0, 6.9 Hz, 2H, Ar-H),
4.85 (dd, $J = 2.9$, 7.0 Hz, 1H, H-2), 3.01 (m, 1H), 3.53 (s, 3H, OMe), 3.01 (dd, $J = 2.1$, 4.5 Hz, 1H), 2.71-2.79 (m, 2H), 2.45(dt, $J = 3.3$, 10.1 Hz, 1H), 2.20 (m, 2H), 1.89 (m, 2H), 1.47 (s, 3H, CH$_3$-7a); $^{13}$C NMR (100.7 MHz, CDCl$_3$) $\delta$ 161.6, 144.3, 142.1, 133.0, 122.7, 119.5, 115.0, 94.9, 84.7, 55.7, 49.2, 44.1, 30.8, 22.4, 22.0; FD-MS m/z = 345 (M)$^+$, Anal. Calcd for C$_{17}$H$_{19}$N$_3$O$_5$ (345.13); C, 59.12; H, 5.55; N, 12.1. Found: C, 59.22; H, 5.67; N, 12.31.

(3b$S$,6$S$,7a$S$)-6-Methoxy-2-(4-methoxyphenyl)-7a-methyl-1,2,3b,4,5,6,7a,8-octahydro-3H-pyrano[3',2':3,4]cyclopenta[1,2-c]pyrazol-3-one (11d). Yield: 110 mg, 82%; $^1$H NMR (400 Mz, CDCl$_3$) $\delta$ 7.61 (dd, $J = 0.9$, 6.5 Hz, 2H, Ar-H), 6.95 (dd, 1.0, $J = 6.5$ Hz, 2H, Ar-H), 4.93 (dd, $J = 2.2$, 6.2 Hz, 1H, H-2), 3.77 (s, 3H, Ar-OMe), 3.00 (m, 1H), 3.40 (s, 3H, OMe), 2.75 (dd, $J = 2.3$, 4.4 Hz, 1H), 1.88 (m, 1H), 2.42(dt, $J = 3.3$, 9.5 Hz, 1H), 2.20 (m, 1H), 1.50 (s, 3H, CH$_3$-7a); $^{13}$C NMR (100.7 MHz, CDCl$_3$) $\delta$ 161.75, 132.5, 132.4, 115.1, 112.6, 94.2, 84.6, 55.7, 55.6, 46.1, 39.8, 32.8, 25.7, 25.2; FD-MS m/z = 330 (M)$^+$, Anal. Calcd for C$_{18}$H$_{22}$N$_2$O$_4$ (330.16); C, 65.44; H, 6.71; N, 8.48, 12.1. Found: C, 65.53; H, 6.65; N, 8.52.

(3b$S$,6$S$,7a$S$)-2-(4-Chlorophenyl)-6-methoxy-7a-methyl-1,2,3b,4,5,6,7a,8-octahydro-3H-pyrano[3',2':3,4]cyclopenta[1,2-c]pyrazol-3-one (11e). Yield: 120.7 mg, 85%; $^1$H-NMR (400 Mz, CDCl$_3$) $\delta$ 7.85 (dd, $J = 0.8$, 6.1 Hz, 2H, Ar-H), 7.30 (dd, 0.9, $J = 6.1$ Hz, 2H, Ar-H), 5.00 (dd, $J = 2.3$, 5.7 Hz, 1H, H-2), 3.03 (m, 1H), 3.99 (s, 3H, OMe), 2.76 (dd, $J = 2.2$, 4.1 Hz, 1H), 2.22-2.46 (m, 3H), 1.89 (m, 3H), 1.47 (s, 3H, CH$_3$-7a); $^{13}$C NMR (100.7 MHz, CDCl$_3$) $\delta$ 160.9, 151.8, 151.3, 139.0, 132.4, 116.8, 115.1, 94.7, 84.6, 55.7, 49.3, 46.1, 30.2, 21.8, 21.4; FD-MS m/z = 334 (M)$^+$, Anal. Calcd for C$_{18}$H$_{19}$ClN$_2$O$_3$ (334.11); C, 60.99; H, 5.72; Cl, 10.59; N, 8.37. Found: C, 60.85; H, 5.79; Cl, 10.61; N, 8.42.

(3b$S$,6$S$,7a$S$)-2-(1H-Indol-2-yl)-6-methoxy-7a-methyl-1,2,3b,4,5,6,7a,8-octahydro-3H-pyrano[3',2':3,4]cyclopenta[1,2-c]pyrazol-3-one (11f). Yield: 98 mg, 76%; $^1$H NMR (400 Mz, CDCl$_3$) $\delta$ 10.62 (bs, 1H), 10.26 (s, 1H), 7.73 (d, $J = 1.8$ Hz, 1H), 7.52 (s, 1H), 7.37 (d, 1H), 7.28-7.12 (m, 5H), 7.08 (s, 1H), 6.98 (d, $J = 1.8$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H). Found: C, 66.48; H, 5.51; N, 8.07; Cl, 10.61; S, 4.12.
\( J = 2.0 \text{ Hz}, 1\text{H}), 7.16 \text{ (t, } J = 1.8, 3.2 \text{ Hz, 1H}), 6.50 \text{ (t, } J = 1.8, 3.3 \text{ Hz, 1H}), 4.84 \text{ (dd, } J = 2.1, 5.2 \text{ Hz, 1H, H-2}), 3.00 \text{ (m, 1H), 3.49 \text{ (s, 3H, OMe), 2.77 \text{ (m, 1H}}, 2.21-2.46 \text{ (m, 2H), 1.88 \text{ (m, 2H), 1.47 \text{ (s, 3H, CH}_3\text{-7a}); FD-MS m/z = 334 (M)+, Anal. Calcd for C}_{19}\text{H}_{21}\text{N}_3\text{O}_3 (339.16); C, 67.24; H, 6.24; N, 12.38. Found: C, 67.33; H, 6.13 N, 12.45.}

(3bS,6\text{S},7\text{aS})-6\text{-Methoxy-7a-methyl-2-pyridin-2-yl-1,2,3b,4,5,6,7a,8-octahydro-3H-pyran-3',2':3,4]cyclopenta[1,2-c]pyrazol-3-one (11g). Yield: 119 mg, 79%\%; \text{^1H NMR (400 Mz, CDCl}_3\text{) 8 8.41 (d, } J = 1.1 \text{ Hz, 1H), 7.92 (d, } J = 0.9 \text{ Hz, 1H), 7.63 (t, } J = 1.3 \text{ Hz, 1H), 6.98 (t, } J = 1.2 \text{ Hz, 1H), 5.19 (t, } J = 4.4 \text{ Hz, 1H, H-2), 3.08 (m, 1H), 3.77 (s, 3H, OMe), 2.65 \text{ (m, 2H), 2.21-2.38 (m, 3H), 1.85 \text{ (m, 2H), 1.42 \text{ (s, 3H, CH}_3\text{-7a); FD-MS m/z = 301 (M)+, Anal. Calcd for C}_{16}\text{H}_{19}\text{N}_3\text{O}_3 (301.14); C, 63.77; H, 6.36; N, 13.94. Found: C, 63.65; H, 6.42; N, 13.81.}

Molecular Modeling. ChemBio3D Ultra 11 was used to calculate the thermodynamicall more preferred conformations of compounds 10 and 10a using force field MM2 method.\textsuperscript{18}

\textit{In vitro cytotoxicity assay.} The cytotoxic activity of the cyclopenta[b]pyrane derivatives 11a-11g was determined using a standard (MTT)-based colorimetric assay.\textsuperscript{12} This assay quantifies viable cells by observing the reduction of tetrazolium salt, MTT, to formazan crystals by the cells. Based on the absorbance of the cell samples after the test is carried out, cell viability can be measured. Cells were plated with nutritional medium in 96 well plates (2000 and 5000 cells/well for HCT116, SK-N-SH and the non-tumorigenic cell line derived from breast tissue (MCF10A)). After 24 hours, cells were treated with different concentrations (0.1, 0.5, 1, 3 and 10 µM) of the new compounds, each concentration in 3 repetitions. The plates were incubated with the pyrazolone derivatives for 72 hours. At the end of treatment, cells were washed with PBS solution. Then, 100 µl of fresh medium and 50 µl from a stock solution of MTT (3mg/ml PBS)
were added to each well. After 4 hours of incubation at 37 °C, the medium was discarded and 100 μl of DMSO solution were added to each well, in order to dissolve the crystals that were formed. After a 30 minute period, the absorbance of the samples was measured by an Elisa reader. The absorbance data were converted to % cell viability. The IC50 were calculated using Graphpad Prism software.
This page contains a diagram with a chemical structure labeled with peaks. The diagram is a spectroscopic analysis, likely an NMR spectrum, showing chemical shifts and integration areas. The peaks are labeled with their corresponding chemical shifts, and the structure includes functional groups such as hydroxyl (OH) and carboxylic acid (COOH).