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Synthesis and Biological Activity of 4,5-Polymethylenepyrazole-derived HMG-CoA Reductase Inhibitors

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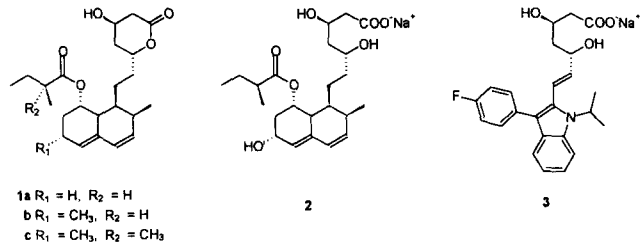
New HMG-CoA reductase inhibitors, in which 3-substituted 4,5-polymethylenepyrazoles are employed as a hydrophobic anchor connected to tetrahydro-4-hydroxy-2H-pyran-2-one by a two-carbon bridge, were designed and synthesized to exhibit significant inhibitory activity comparable to mevinolin. The most potent enzyme inhibitor (**11cc**, IC_{50}=0.01 μM) is 4-fold more potent than lovastatin.

Keywords : HMG-CoA reductase inhibitor, 3-Substituted 4,5-polymethylenepyrazole

INTRODUCTION

Controlling *de novo* synthesis of cholesterol by selective inhibition of biosynthetic step has been one of the effective ways to lower plasma cholesterol level. Inhibition of the later steps in cholesterol biosynthesis, however, causes accumulation of sterol intermediates resulting serious adverse effects (Ariens, 1963). Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, therefore, is the choice in controlling *de novo* synthesis of cholesterol. The discoveries of fungal metabolite, compactin (**1a**) (Endo *et al.*, 1976; Brown *et al.*, 1976) opened a new era for the treatment of hypercholesterolemia by inhibiting cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The HMG-CoA reductase inhibitors have proven to be effective agents for the treatment of hypercholesterolemia by lowering not only total cholesterol but also low density lipoprotein (LDL) cholesterol (Illingworth, 1991). The fungal metabolites, lovastatin (**1b**) (Endo, 1979; Alberts *et al.*, 1980) and pravastatin (**2**) (Tsujita, *et al.*, 1986), as well as the semisynthetic simvastatin (**1c**) (Hoffman, *et al.*, 1986) have approved in USA for clinical use.

The structure-activity relationship (SAR) studies upon these molecules as well as related compounds revealed that potent inhibitors share the essential chiral β-hydroxy-δ-lactone moiety (or its equivalent *syn*-3,5-dihydroxyheptanoic acid) linking unit (usually -CH_2 CH_2- or *trans*-CH=CH-), and a replaceable planar aromatic ring with suitable substituents (more likely 4-fluorophenyl) (Stokker *et al.*, 1986; Jendralla *et al.*, 1991, Jahng, 1995). The aromatic rings served for the replacement of dehydrodecalin moiety of **1**, include carbocycles, nitrogen- and/or oxygen-containing heterocycles without losing the activity in the case that such a moiety can impose suitable physicochemical factors in binding inhibitors to the enzyme (Roth *et al.*, 1989 and 1991). Finding of totally synthetic fluvastatin (**3**), currently used in clinic, culminates the synthetic approach on the introduction of nitrogen-containing heterocycles (Kasawala, 1989). We, herein, present the synthesis and biological activity of a new series of compounds, in which 3-substituted 4,5-polymethylenepyrazole nucleus is expected to provide appropriate steric and physicochemical features.



1a R_1 = H, R_2 = H
b R_1 = CH_3, R_2 = H
c R_1 = CH_3, R_2 = CH_3

2

3

MATERIALS AND METHODS

Melting points were determined on Fisher-Jones melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin Elmer 1310 spectrophotometer in KBr, except where noted. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM-300 (300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR) spectrometer and chemical shifts are reported in parts per million (ppm) downfield from

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tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933 A GC-mass spectrometer and are reported herein as *m/e* (relative intensity). Dry DMF was obtained by distilling over CaH_2, dry THF was obtained by distilling over sodium benzophenone ketyl, and all other solvents were reagent grade and used directly without further purification. 2-Acylcycloalkanones were prepared by previously reported method or modification of such a method (Szmuszkovicz and Skaletzky, 1967).

General Procedure

3-Substituted 4,5-Polymethylenepyrazoles (Ainsworth, 1963): To a cooled solution of 0.03 mol of 2-acylcycloalkanone in 40 mL of MeOH was slowly added 0.048 mmol of 80% hydrazine hydrate at 0°C. The resulting mixture was stirred for 40 min and concentrated to afford crystalline solid, which is pure enough to employ for the next reaction.

Synthesis of Acetals: To a suspension of 10 mmol of 50% NaH in 10 mL of dry DMF was added a solution of 10 mmol of 3-substituted 4,5-polymethylenepyrazole in 10 mL of DMF under N_2. When the gas evolution had ceased, 2.5 mmol of NaI was added, followed by the dropwise addition of 1.67 g (0.01 mol) of 3-chloropropionaldehyde diethyl acetal in 10 mL of DMF. The resulting solution was heated at 85°C for 60 h. The reaction mixture was poured into 100 mL of ice-water and extracted with ether (3×50 mL). Work-up as usual gave a crude material, which was chromatographed on silica gel, eluting with *n*-hexane: EtOAc (1:1). The early fractions afforded N_2-alkylated product (**6**) and the latter fractions afforded N_1-alkylated product (**5**).

Synthesis of 3-Substd. Propanals: A solution of 2.0 mmol of acetal **5** and 0.42 g (2.2 mmol) of *p*-TsOH·H_2O in 20 mL of acetone-water (5:1) was refluxed for 48 h. The cooled mixture was concentrated and extracted with Et_2O (3×50 mL). The combined organic layer was washed with satd. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave a crude material, which was chromatographed on silica gel, eluting with *n*-hexane: CH_2Cl_2 (2:3). The early fractions afforded 3-(3-substd 4,5-polymethylenepyrazolyl)propanals.

Synthesis of 5-Hydroxy-3-oxo-heptanoates (Condensation of Aldehyde with Dianion): To a chilled mixture of 0.24 g (0.37 mmol, 60% suspension in mineral oil) of NaH in 100 mL of dry THF under N_2 atmosphere, was added 0.49 g (0.38 mmol) of ethyl acetoacetate in 10 min. The homogeneous, clear solution was stirred at 0°C for 30 min, followed by the dropwise addition 3.93 mL (0.37 mmol) of *n*-BuLi in hexane (1.6 mol) solution over 15 min. The orange anion solution was stirred at 0°C for an additional hour. The acetone-dry ice bath was controlled at -78°C and a THF solution containing 0.37 mmol of aldehyde **7** was added with stirring at -78°C for 1 h. The mixture was, then, diluted with 0.5 N HCl solution (until pH=5), and extracted with Et_2O (3×50 mL). The combined organic layer was washed with H_2O, satd. $NaHCO_3$, and dried over anhyd. $MgSO_4$. Concentration under reduced pressure gave a crude material, which was chromatographed on silica gel, eluting with *n*-hexane: CH_2Cl_2 (3:2). The latter fractions gave a pale yellow oil.

Synthesis of *cis*-3,5-Dihydroxy Acids: To a solution of 0.06 mmol of 3-oxo-5-hydroxy ester **8** in 20 mL of dry THF at 0°C under Ar atmosphere, was added 0.6 mL (0.06 mmol) of 1M triethylborane solution in THF in one portion. The cooling ice-water bath was replaced with an acetone-dry ice bath, and then to the reaction mixture was added 0.03 g (0.72 mmol) of $NaBH_4$ in one portion. The reaction suspension was stirred at -78°C for 2 h, forming a clear, homogeneous pale yellow solution. The reaction mixture was diluted with 0.8 mL of CH_3OH and the solution was allowed to stir at -78°C for an additional 1.5 h. The reaction mixture was, then, diluted with 100 mL of 1N HCl, followed by extractions with ether (3×50 mL). The combined organic layer was washed with H_2O, dried over $MgSO_4$, concentrated under reduced pressure to give a crude product as a thick syrup. The crude syrup was chromatographed on silica gel, eluting with *n*-hexane: $CHCl_3$ (4:1). The later fractions afforded dihydroxy compounds **9** as a red oil.

Hydrolysis of Esters: To the solution containing 0.23 mmol of dihydroxy ester **8** in 15 mL of THF was added 1.42 mL of MeOH and followed by the dropwise addition of 4 mL of 3N LiOH. The resulting solution was allowed to be stirred overnight. To the reaction mixture was added 50 mL of Et_2O and stirred for additional 20 min. The organic layer was separated and the aq. phase was diluted with 5 mL of H_2O and extraced with 50 mL of Et_2O. The organic layer was washed with 2N LiOH and the aq. layer was separated. The combined aqueous layer was acidified with 6 N HCl (pH=3) and extracted with EtOAc (3×100 mL). The combined organic layer was washed with saline, dried over $MgSO_4$. The removal of the solvent afforded corresponding acid as a white solid.

Synthesis of Lactones: To the solution of 0.22 mmol of dried *cis*-7-(3-substd. 4,5-polymethylenepyrazol-1-yl)-3,5-dihydroxyheptanoic acid in 20 mL of CH_2Cl_2 was added 1.40 g (0.66 mmol) of DCC and the resulting mixture was allowed to be stirred for 8 h. After removing the solvent, the resulting solid was dissolved in minimum amount of water, and extracted with Et_2O (3×70 mL). The oily material was purified by column chromatography, eluting with CH_2Cl_2. The latter frac-

tions afforded the product as a crystalline solid.

3-Phenyl-4,5-trimethylenepyrazole (4ab)

White crystals (75%), mp 126-128°C: IR (KBr) 2920, 2840, 1590, 1445, 1370, 1060, 1040, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.75 (br. s, NH), 7.60 (dd, 2H, J=7.3, 1.2 Hz), 7.33 (td, 2H, J=7.3, 1.2 Hz), 7.23 (td, 1H, J=7.3, 1.2 Hz), 2.78 (t, 2H, J=6.8 Hz), 2.67 (t, 2H, J=6.8 Hz), 2.45 (quintet, 2H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 130.7, 128.7 (2 C's), 127.3, 125.4 (2 C's), 122.9, 30.5, 24.2, 24.0.

3-(4-Fluorophenyl)-4,5-trimethylenepyrazole (4ac)

White crystals (85%), mp 152-155°C: IR (KBr) 2920, 1590, 1490, 1430, 1370, 1310, 1265, 1220, 1145, 1100, 1090, 985, 930, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.45 (br. s, NH), 7.67 (dd, J=8.6, 5.5 Hz), 7.15 (t, 2H, J=8.8 Hz), 2.78 (t, 2H), 2.66 (t, 2H), 2.51 (quintet, 2H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.1 (d, $^1J_{C-F}$=245 Hz), 151.8, 143.8, 130.3, 128.5 (d, $^3J_{C-F}$=8 Hz), 121.4, 115.2 (d, $^2J_{C-F}$=21 Hz), 30.1, 23.4 (2 C's).

3-Phenyl-4,5-tetramethylenepyrazole (4bb)

White crystals (86%), mp 118-121°C: IR (KBr) 3020, 2920, 1550, 1440, 1350, 1300, 1260, 1150, 1050, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.76 (br. s, NH), 7.60 (dd, 2H, J=7.3, 1.2 Hz), 7.33 (td, 2H, J=7.3, 1.0 Hz), 7.27 (td, 1H, J=7.3, 1.0 Hz), 2.70 (t, 2H, J=5.8 Hz), 2.63 (t, 2H, J=5.8 Hz), 1.80 (m, 4H, H_5 & H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 144.3, 131.7, 128.5, 127.3, 126.9, 126.4, 112.9, 23.5, 22.6, 22.2, 22.0.

3-(4-Fluorophenyl)-4,5-tetramethylenepyrazole (4bc)

White crystals (85%), mp 142-143°C: IR (KBr) 3150, 3050, 2900, 1590, 1430, 1220, 1140, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.54 (br. s, NH), 7.55 (dd, 2H), 7.00 (dd, 2H, J=8.7, 1.8 Hz), 2.64 (t, 2H), 2.52 (t, 2H, J=5.3 Hz), 1.74 (overlapped t, 4H, J=5.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.6 (d, $^1J_{C-F}$= 245 Hz), 146.4, 139.4, 129.4, 128.2 (d, $^3J_{C-F}$=8 Hz), 115.3 (d, $^2J_{C-F}$=21 Hz), 112.6, 23.5, 22.5, 21.9 (2 C's).

3-(4-Phenyl)-4,5-pentamethylenepyrazole (4cb)

White crystals (85%), mp 181-183°C: IR (KBr) 3030, 2920, 1580, 1430, 1370, 1220, 1100, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 7.46 (dd, 2H, J=7.3, 1.2 Hz), 7.35 (td, 2H, J=7.3, 1.0 Hz), 7.28 (td, 1H, J=7.3, 1.0 Hz), 2.68 (m, 4H), 1.82-1.79 (m, 2H), 1.66-1.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 75., 5 MHz) δ 149.5, 143.3, 132.8, 128.3, 128.2, 127.3, 117.2, 32.1, 29.0, 28.2, 27.4, 24.7.

3-(4-Fluorophenyl)-4,5-pentamethylenepyrazole (4cc)

White crystals (88%), mp 154-155°C: IR (KBr) 3040, 2900, 2840, 1590, 1440, 1430, 1260, 1215, 1145, 1085, 980, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.05 (br. s, NH), 7.39 (dd, 2H, J=8.7, 2.0 Hz), 7.01 (td, 2H, J=8.7, 2.0 Hz), 2.57 (m, 4H), 1.78-1.81 (m, 2H), 1.59-1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.4 (d, $^1J_{C-F}$=246 Hz), 148.3, 143.4, 130.0 (d, $^3J_{C-F}$= 7.7 Hz), 117.3, 115.3 (d, $^2J_{C-F}$=21 Hz), 32.0, 29.0, 27.6, 27.3, 24.7.

3-(4-Phenyl)-4,5-hexamethylenepyrazole (4db)

White crystals (86%), mp 125°C: IR (KBr) 3030, 2850, 1430, 1250, 1050, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 7.54 (dd, 2H, J=7.3, 1.5 Hz), 7.42-7.25 (m, 3H), 2.73 (t, 2H, J=6.5 Hz), 2.68 (t, 2H, J=6.5 Hz), 1.75-1.68 (m, 4H), 1.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.,5 MHz) δ 149.5, 143.3, 132.8, 128.6, 128.6, 127.3, 117.2, 30.3, 28.8, 25.8, 25.6, 24.9, 21.7.

3-(4-Fluorophenyl)-4,5-hexamethylenepyrazole (4dc)

White crystals (83%), mp 129-130°C: IR (KBr) 3080, 2850, 1420, 1195, 1130, 1080, 980, 960, 935, 800, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.05 (br. s, NH), 7.49 (dd, 2H, J=8.7, 2.0 Hz), 7.09 (td, 2H, J=8.7, 2.0 Hz), 2.70 (m, 4H), 2.64 (t, 2H, J=6.4 Hz), 1.69 (m, 4H), 1.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.4 (d, $^1J_{C-F}$=246 Hz), 148.3, 143.4, 129.4 (d, $^3J_{C-F}$= 7.7 Hz), 117.3, 115.4 (d, $^2J_{C-F}$=21 Hz), 115.1, 30.2, 29.5, 25.8, 25.6, 24.8, 21.7.

1-(3,3-Diethoxypropyl)-3-phenyl-4,5-trimethylenepyrazole (5ab)

Pale yellow oil (80%): IR (thin film) 2900, 1630, 1430, 1380, 1240, 1090, 1050, 720, 690, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (dd, 2H, J=7.3, 1.3 Hz), 7.37 (dd, 2H, J=7.3, 1.4 Hz), 7.23 (td, 1H), 4.50 (t, 1H, J=5.7 Hz, H_3), 4.09 (t, 2H, J=7.2 Hz, H_1), 3.65 (q, 2H, J=7.0 Hz, OCH_2), 3.50 (q, 2H, J=7.0 Hz, OCH_2), 2.85 (dd, 2H, J=6.9, 5.8 Hz), 2.72-2.65 (m, 2H), 2.63-2.61 (m, 2H), 2.17 (td, 2H, J=7.0, 5.7 Hz), 1.20 (t, 6H, J=7.0 Hz).

1-(3,3-Diethoxypropyl)-3-(4-fluorophenyl)-4,5-trimethylenepyrazole (5ac)

Pale yellow oil (75%): IR (thin film) 2900, 1630, 1430, 1370, 1250, 1090, 1050, 830, 720, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (dd, 2H, J=8.8, 5.4 Hz), 7.03 (dd, 2H), 4.50 (t, 1H, J=5.7 Hz, H_3), 4.07 (t, 2H, J=7.2 Hz, H1), 3.65 (q, 2H, J=7.0 Hz, OCH_2), 3.49 (q, 2H, J=7.0 Hz, OCH_2), 2.81-2.77 (m, 2H), 2.70-2.68 (m, 2H), 2.63-2.60 (m, 2H), 2.28 (td, 2H, J=7.1, 6.0 Hz), 1.20 (t, 6H, J=7.0 Hz).

1-(3,3-Diethoxypropyl)-3-phenyl-4,5-tetramethylenepyrazole (5bb)

Pale yellow oil (65%): IR (thin film) 3040, 2900, 1430, 1360, 1110, 1050, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (dd, 2H, J=7.3, 1.0 Hz), 7.36 (td, 2H, J=7.3, 1.0), 7.25 (t, 1H), 4.51 (t, 1H, J=5.6 Hz, $H_{3'}$), 4.09 (t, 2H, J=7.0 Hz, $H_{1'}$), 3.67-3.62 (m, 2H, OCH_2), 3.53-3.46 (m, 2H, OCH_2), 2.71 (t, 2H, J=5.9 Hz), 2.62 (t, 2H, J=6.2 Hz), 2.19 (dt, 2H, J=6.9, 6.0 Hz, $H_{2'}$), 1. 90-1.86 (m, 2H), 1.78-1.76 (m, 2H), 1.21 (t, 6H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 147.2, 139.2, 134.7, 128.3, 126.8, 126.6, 113.3, 100.7, 61.6, 61.4, 44.4, 34.2, 23.4, 22.48, 22.46, 21.6, 15.3, 15.1.

1-(3,3-Diethoxypropyl)-3-(4-fluorophenyl)-4,5-tetramethylenepyrazole (5bc)

Pale yellow oil (80%): IR (thin film) 2900, 1630, 1430, 1380, 1240, 1090, 1050, 720, 690, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (dd, 2H, J=8.9, 5.7 Hz), 7.04 (dd, 2H), 4.49 (t, 1H, J=5.7 Hz, H_3), 4.06 (t, 2H, J=6.9 Hz, H_1), 3.64 (q, 2H, J=7.0 Hz, OCH_2), 3.48 (q, 2H, J=7.0 Hz, OCH_2), 2.64 (t, 2H, J=6.0 Hz), 2.59 (t, 2H, J=6.0 Hz), 2.16 (td, 2H, J=6.9, 6.0 Hz, H_2), 1.84-1.73 (m, 4H), 1.18 (t, 6H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.0 (d, $^1J_{C-F}$=246 Hz), 146.4, 139.4, 130.8, 128.2 (d, $^3J_{C-F}$=8 Hz), 115.2 (d, $^2J_{C-F}$=25 Hz), 113.0, 100.6, 61.5, 44.3, 34.1, 23.3, 22.4, 22.3, 21.5, 15.2.

1-(3,3-Diethoxypropyl)-3-phenyl-4,5-pentamethylenepyrazole (5cb)

Pale yellow oil (66%): IR (thin film) 2900, 1600, 1410, 1270, 1120, 1090, 720, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (dd, 2H, J=7.0, 1.5 Hz), 7.34 (t, 3H, J=7.0 Hz), 7.29 (m, 1H), 4.52 (t, 1H, J=5.6 Hz), 4.12 (t, 2H, J=7.0 Hz), 3.60 (q, 2H, J=7.0 Hz), 3.45 (q, 2H, J=7.0 Hz), 2.73 (t, 2H, J=7.0 Hz), 2.57 (t, 2H, J=7.0 Hz), 2.15 (m, 2H), 1.83-1.48 (m, 6H), 1.16 (t, 6H, J= 7.0 Hz).

1-(3,3-Diethoxypropyl)-3-(4-fluorophenyl)-4,5-pentamethylenepyrazole (5cc)

Pale yellow oil (67%): IR (thin film) 3040, 2900, 1600, 1430, 1360, 1250, 1090, 1050, 730, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.42 (m, 2H), 7. 04-6.98 (m, 2H), 4.48 (t, 1H, J=5.7 Hz, H_3), 4.12 (t, 2H, J=7.0 Hz, H_1), 3.60 (q, 2H, J=6.7 Hz, OCH_2), 3.48 (q, 2H, J=6.7 Hz, OCH_2), 2.78-2.69 (m, 2H), 2.63-2.57 (m, 2H), 2.12-2.05 (m, 2H), 1.85-1.75 (m, 2H), 1.74-1.48 (m, 4H), 1.16 (t, 6H).

1-(3,3-Diethoxypropyl)-3-phenyl-4,5-hexamethylenepyrazole (5db)

Pale yellow oil (66%): IR (thin film) 3010, 2890, 1430, 1360, 1340, 1250, 1100, 1040, 720, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.62 (dd, 2H, J=7.2, 1.5 Hz), 7.35 (t, 2H, J=7.2 Hz), 7.27 (dd, 1H, J=7.2, 2.0 Hz), 4.52 (t, 1H, J=5.6 Hz), 4.13 (t, 2H, J=7.0 Hz), 3.60 (q, 2H, J=7.0 Hz), 3.45 (q, 2H, J=7.0 Hz), 2.74 (t, 2H, J =7.0 Hz), 2.66 (t, 2H, J=7.0 Hz), 2.18 (m, 2H), 1.70 (m, 4H), 1.49 (m, 2H), 1.16 (t, 6H, J=7.0 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 148.2, 140.6, 134.5, 128.0, 127.5, 126.7, 115.4, 100.6, 61.4, 44.3, 34.5, 30.5, 28.0, 25.7, 25.3, 22.7, 22.5.

1-(3,3-Diethoxypropyl)-3-(4-fluorophenyl)-4,5-hexamethylenepyrazole (5dc)

Pale yellow oil (71%): IR (thin film) 3050, 2920, 1440, 1260, 1120, 1050, 890, 840, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (dd, 2H, J=8.6, 2.0 Hz), 7.06 (td, 2H, J=8.6, 2.0 Hz), 4.52 (t, 1H, J=5.7 Hz, H_3), 4.13 (t, 2H, J=7.0 Hz, H_1), 3.65 (q, 2H, J=6.7 Hz, OCH_2), 3.50 (q, 2H, J=6.7 Hz, OCH_2), 2.76 (t, 2H, J=6.4 Hz), 2.63 (t, 2H, J=6.4 Hz), 2.18 (m, 2H), 1.70-1.67 (m, 4H), 1.50-1.48 (m, 4H), 1.20 (t, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.1 (d, $^1J_{C-F}$=243 Hz), 147.6, 140.9, 130.8 (d, $^4J_{C-F}$=3 Hz), 129.3 (d, $^3J_{C-F}$=7.8 Hz), 115.5, 115.0 (d, $^2J_{C-F}$=21 Hz), 100.7, 61.6, 44.5, 34.7, 30.6, 28.2, 25.9, 25.5, 22.9, 22.6, 15.2.

3-(3-Phenyl-4,5-trimethylenepyrazol-1-yl)propanal (7ab)

Colorless oil (57%): IR (thin film) 2900, 1700, 1430, 1280, 1050, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, -CHO), 7.71 (dd, 2H, J=7.3, 1.4 Hz), 7.34 (dd, 2H, J=7.3, 2.4), 7.25 (td, 1H), 4.30 (t, 2H, J= 6.7 Hz, H_3), 3.07 (td, 2H, J=7.2, 6.7 Hz, H_2), 2.84-2.80 (m, 2H), 2.76-2.71 (m, 2H), 2.64-2.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 199.5, 151.5, 144.7, 134.0, 128.5, 127.1, 125.7, 124.3, 43.6, 43.3, 30.9, 24.7, 23.5.

3-[3-(4-Fluorophenyl)-4,5-trimethylenepyrazol-1-yl] propanal (7ac)

White powder (42%), mp 62-63°C: IR (thin film) 2900, 1700, 1430, 1210, 830, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.83 (s, -CHO), 7.68-7.64 (m, 2H), 7.06-7.00 (m, 2H), 4.29 (t, 2H, J=6.6 Hz, H_3), 3.08 (dt, 2H, J= 7.2, 6.7 Hz, H_2), 2.82-2.77 (m, 2H), 2.74-2.70 (m, 2H), 2.63-2.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 199.4, 162.1 (d, $^1J_{C-F}$=246 Hz), 151.7, 143.9, 130.3, 127.2 (d, $^3J_{C-F}$=8 Hz), 123.7, 115.4 (d, $^2J_{C-F}$=22 Hz), 43.6, 43.4, 31.0, 24.6, 23.6.

3-(3-Phenyl-4,5-tetramethylenepyrazol-1-yl)propanal (7bb)

White powder (88%), mp 100-101°C: IR (thin film) 2900, 1700, 1430, 1280, 1050, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, -CHO), 7.69 (dd,

2H, J=7.3, 1.3 Hz), 7.36 (dd, 2H, J=7.3, 1.8 Hz), 7.24 (td, 1H), 4.28 (t, 2H, J=6.7 Hz, H3), 3.07 (t, 2H, J=6.6 Hz), 2.69 (t, 2H, J=6.0 Hz), 2.63 (t, 2H, J=6.6 Hz), 1.87-1.81 (m, 2H), 1.78-1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 199.7, 147.6, 139.5, 134.4, 128.4, 127.0, 126.6, 113.5, 43.5, 41.5, 23.3, 22.3 (two C's), 21.5.

3-[3-(4-Fluorophenyl)-4,5-tetramethylenepyrazol-1-yl] propanal (7bc)

White solid (48%), mp 89-90°C: IR (thin film) 2900, 2840, 1700, 1520, 1430, 1210, 1150, 830, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.83 (s, -CHO), 7.66-7.61 (m, 2H), 7.07-7.01 (m, 2H), 4.28 (t, 2H, J=6.6 Hz, H_3), 3.07 (td, 2H, J=6.6, 0.9 Hz), 2.65 (t, 2H, J=6.2 Hz), 2.63 (t, 2H, J=6.3 Hz), 1.88-1.81 (m, 2H), 1.78-1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 199.4, 162.1 (d, $^1J_{C-F}$=246 Hz), 146.6, 139.7, 130.5, 128.3 (d, $^3J_{C-F}$=8 Hz), 115.3 (d, $^2J_{C-F}$=21 Hz), 113.4, 43.4, 41.5, 23.2, 22.3, 22.2, 21.5.

3-(3-Phenyl-4,5-pentamethylenepyrazol-1-yl)propanal (7cb)

Pale yellow oil (50%): IR (thin film) 3060, 2900, 1700, 1430, 1370, 1260, 1060, 765, 730, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, -CHO), 7.50 (dd, 2H, J=7.0, 1.8 Hz), 7.40 (td, 2H, J=7.0, 1.8 Hz), 7.27 (td, 1H), 4.36 (t, 2H, J=6.6 Hz, H_3), 3.04 (t, 2H, J=7.0 Hz), 2.78-2.75 (m, 2H), 2.68-2.64 (m, 2H), 1.85-1.80 (m, 2H), 1.77-1.70 (m, 2H), 1.68-1.61 (m, 2H).

3-[3-(4-Fluorophenyl)-4,5-pentamethylenepyrazol-1-yl]propanal (7cc)

Pale yellow oil (73%): IR (thin film) 2900, 1700, 1600, 1440, 1210, 1080, 830, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (t, J=1.0 Hz, -CHO), 7.46-7.41 (m, 2H), 7.07-7.01 (m, 2H), 4.35 (t, 2H, J=6.7 Hz, H_3), 3.01(td, 2H, J=6.8, 1.0 Hz, H_2), 2.78-2.73 (m, 2H), 2.62-2.58 (m, 2H), 1.85-1.78 (m, 2H), 1.76-1.65 (m, 2H), 1.65-1.62 (m, 2H).

3-(3-Phenyl-4,5-hexamethylenepyrazol-1-yl)propanal (7db)

Pale yellow oil (93%): IR (thin film) 3020, 2890, 2730, 1690, 1580, 1430, 1280, 1250, 1050, 930, 860, 720, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.80 (s, 1H, CHO), 7.59 (dd, 2H, J=7.1, 2.1 Hz), 7.37 (td, 2H, J= 7.1, 2.1 Hz), 7.37 (td, 2H, J=7.1, 2.0 Hz), 4.34 (t, 2H, J=6.6 Hz), 3.05 (t, 2H, J=6.7 Hz), 2.76 (t, 2H, J=6.1 Hz), 2.65 (t, 2H, J=6.1 Hz), 1.73-1.68 (m, 4H), 1.31 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 199.6, 148.6, 140. 1, 134.3, 128.2, 127.7, 127.0, 115.9, 43.6, 41.7, 30.5, 28.0, 25.8, 25.3, 22.8, 22.6.

3-[3-(4-Fluorophenyl)-4,5-hexamethylenepyrazol-1-yl] propanal (7dc)

Pale yellow oil (83%): IR (thin film) 3020, 2890, 2730, 1690, 1580, 1430, 1280, 1205, 1140, 1070, 990, 930, 825, 790, 730, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.90 (s, 1H, CHO), 7.53 (dd, 2H, J=8.6, 2.0 Hz), 7.06 (dd, 2H, J=8.6, 2.0 Hz), 4.35 (t, 2H, J=6.7 Hz), 3.08 (t, 2H, J=6.7 Hz), 2.78 (t, 2H, J=6.1 Hz), 2.63 (t, 2H, J=6.1 Hz), 1.73-1.68 (m, 4H), 1.50-1.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) 199.6, 162.2 (d, $^2J_{C-F}$=244 Hz), 148.0, 141.2, 130.5 (d, $^4J_{C-F}$=3 Hz), 129.2 (d, $^3J_{C-F}$=7.8 Hz), 115.9, 115.2 (d, $^2J_{C-F}$=21 Hz), 43.7, 41.8, 30.6, 28.1, 25.9, 25.4, 22.9, 22.6.

(±)-Ethyl 7-(3-phenyl-4,5-trimethylenepyrazol-1-yl)-5-hydroxy-3-oxo-heptanoate (8ab)

Pale yellow oil (71%): IR (thin film) 3400, 2900, 1430, 1250, 1020, 740, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (dd, 2H, J=7.5, 1.0 Hz), 7.38 (td, 2H), 7.26 (td, 1H), 4.22-4.11 (m, 3H), 4.15 (q, 2H, OCH_2), 3.47 (s, 2H, H_2), 2.88-2.83 (m, 2H), 2.78-2.69 (m, 2H), 2.66-2.64 (m, 2H), 2.56-2.45 (m, 2H), 2.13-2.06 (m, 1H), 1.95-1.85 (m, 1H), 1.25 (t, 3H).

(±)-Ethyl 7-[3-(4-fluorophenyl)-4,5-trimethylenepyrazol-1-yl]-5-hydroxy-3-oxo-heptanoate (8ac)

Pale yellow oil (69%): IR (thin film) 3400, 2900, 1700, 1600, 1430, 1220, 1140, 830, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.63 (m, 2H), 7.06-7.00 (m, 2H), 4.20-4.09 (m, 3H), 4.17 (q, 2H, J=7.2 Hz, OCH_2), 3.45 (s, 2H, H_2), 2.84-2.80 (m, 2H), 2.73-2.68 (m, 4H), 2.65-2.59 (m, 2H), 1.96-1.87 (m, 2H), 1.24 (t, 3H); Mass spectrum, m/e (rel. intensity) 389 (2.5, M+1), 388 (19.5, M), 370 (5, M-H_2O), 343 (10), 298 (12), 273 (55), 255 (23), 230 (22), 216 (36), 215 (100), 203 (48), 202 (82), 133 (10), 122 (14).

(±)-Ethyl 7-[3-phenyl-4,5-tetramethylenepyrazol-1-yl)-5-hydroxy-3-oxo-heptanoate (8bb)

Pale yellow oil (72%): IR (thin film) 3380, 2900, 1700, 1430, 1250, 1020, 730, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (dd, 2H, J=7.3, 1.4 Hz), 7.38 (dd, 2H, J= 7.3, 2.1 Hz), 7.27 (td, 1H), 4.23-4.08 (m, 3H), 4.15 (q, 2H, J=7.2 Hz, OCH_2), 3.47 (s, 2H, H_2), 2.79-2.68 (m, 4H), 2.64-2.61 (m, 2H), 2.07-2.03 (m, 1H), 1.91-1.80 (m, 2H), 1.79-1.75 (m, 2H), 1.26 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 202.8, 167.0, 147.4, 140.0, 134.1, 128.4, 127.1, 126.6, 113.7, 65.4, 61.4, 49.9, 49.7, 45.1, 36.6, 23.3, 22.6, 22.3, 21.5, 14.0; Mass spectrum, m/e (rel. intensity) 385 (1.9, M+ 1), 384 (5.0, M), 366 (3.6), 339 (4.4), 294 (42), 251 (65), 211 (100), 199 (15), 170 (21).

(±)-Ethyl 7-[3-(4-fluorophenyl)-4,5-tetramethylenepyrazol-1-yl]-5-hydroxy-3-oxo-heptanoate (8bc)

Colorless oil (76%): IR (thin film) 3380, 2920, 2840,

1700, 1600, 1430, 1300, 1220, 1140, 1020, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66-7.59 (m, 2H), 7.07-7.02 (m, 2H), 4.22-4.08 (m, 3H), 4.17 (q, 2H, J= 7.1 Hz, OCH_2), 3.46 (s, 2H, H_2), 2.73-2.59 (m, 6H), 2.15-2.03 (m, 2H), 1.91-1.76 (m, 4H), 1.24 (t, 3H, J= 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 202.7, 167.0, 162.2 (d, $C_{4'}$, $^1J_{C-F}$=246 Hz), 146.6, 140.0, 130.4, 128. 3 (d, $C_{2'\ \&\ 6'}$, $^3J_{C-F}$=8 Hz), 115.4 (d, $C_{3'\ \&\ 5'}$, $^2J_{C-F}$=22 Hz), 65.3, 61.3, 49.9, 49.8, 45.1, 36.5, 23.2, 22.3, 22.2, 21.5, 14.0.

(±)-Ethyl 7-(3-phenyl-4,5-pentamethylenepyrazol-1-yl)-5-hydroxy-3-oxo-heptanoate (8cb)

Pale yellow oil (76%): IR (thin film) 3400, 2900, 1700, 1440, 1260, 1020, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48 (dd, 2H, J=7.0, 1.2 Hz), 7.40 (dd, 2H, J= 7.0, 1.3 Hz), 7.26 (td, 1H), 4.25 (m, 1H), 4.20-4.16 (m, 2H), 4.17 (q, 2H, J=7.1 Hz, OCH_2), 3.46 (s, 2H, H $_2$), 2.78-2.74 (m, 2H), 2.67-2.65 (m, 2H), 2.05-1.98 (m, 1H), 1.87-1.82 (m, 3H), 1.75-1.64 (m, 6H), 1.27 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 202.8, 167.0, 153.2, 143.2, 130.0, 128.7, 128.4, 128.2, 119.4, 65.1, 61.3, 49.9, 49.8, 45.4, 36.8, 31.6, 29.3, 28.4, 26.1, 24.8, 14.0.

(±)-Ethyl 7-[3-(4-fluorophenyl)-4,5-pentamethylene-pyrazol-1-yl]-5-hydroxy-3-oxo-heptanoate (8cc)

Colorless oil (82%): IR (thin film) 3400, 2900, 2840, 1700, 1600, 1430, 1300, 1220, 1140, 1020, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.38 (m, 2H), 7.13-7.02 (m, 2H), 4.26-4.18 (m, 1H), 4.17 (q, 2H, OCH_2), 4.11-4.03 (m, 2H), 3.45 (s, 2H, H_2), 2.76-2.73 (m, 2H), 2.70-2.60 (m, 4H), 1.89-1.80 (m, 4H), 1.77-1.60 (m, 4H), 1.24 (t, 3H)

(±)-Ethyl 7-(3-phenyl-4,5-hexamethylenepyrazol-1-yl)-5-hydroxy-3-oxo-heptanoate (8db)

Colorless oil (93%): IR (thin film) 3500-3100, 3040, 2910, 1700, 1430, 1260, 1030, 890, 730, 690 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57 (dd, 2H, J=7.3, 2.0 Hz), 7.37 (td, 2H, J=7.3, 2.1 Hz), 7.29 (td, 1H, J=7.3, 2.0 Hz), 4.28-4.12 (m, 5H, $-OCH_2-$, $-NCH_2-$ and OH), 4.08-4.04 (m, 1H), 3.46 (s, 2H, H_2), 2.78-2.64 (m, 6H), 2.08-2.02 (m, 1H), 1.89-1.84 (m, 1H), 1.72 (m, 4H), 1.50 (m, 4H), 1.25 (t, 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 202.7, 166.9, 148.6, 141.4, 134.1, 128.3, 127.8, 127.2, 116.0, 65.4, 61.3, 49.9, 49.7, 45.3, 36.8, 30.6, 28.3, 25.9, 25.5, 22.9, 22.7, 14.0.

(±)-Ethyl 7-[3-(4-fluorophenyl)-4,5-hexamethylenepy-razol-1-yl]-5-hydroxy-3-oxo-heptanoate (8dc)

Colorless oil (89%): IR (thin film) 3500-3040, 2920, 1700, 1520, 1490, 1360, 1300, 1220, 1090, 900, 830, 720, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53 (dd, 2H, J=8.7, 2.0 Hz), 7.07 (dd, 2H, J=8.7, 2.1 Hz), 4.26-4.12 (m, 5H, $-OCH_2-$, $-NCH_2-$ and OH), 4.07-4.04 (m, 1H, H_5), 3.46 (s, 2H, H_2), 2.77-2.61 (m, 6H), 2.03 (m, 1H), 1.88-1.85 (m, 1H), 1.70 (m, 4H), 1.50 (m, 4H), 1.25 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 202.6, 166.8, 162.2 (d, $^1J_{C-F}$=246 Hz), 147.6, 141.4, 130.2 (d, $^4J_{C-F}$=3 Hz), 129.3 (d, $^3J_{C-F}$=7.8 Hz), 115.8, 115.2 (d, $^2J_{C-F}$=22 Hz), 65.2, 61.2, 49.8, 49.6, 45.3, 36.8, 30.5, 28.2, 25.8, 25.4, 22.8, 22.5, 13.9.

(±)-Ethyl *cis*-7-(3-phenyl-4,5-trimethylenepyrazol-1-yl)-3,5-dihydroxyheptanoate (9ab)

Colorless oil (95%): IR (thin film) 3450, 2900, 1700, 1440, 1300, 1140, 1080, 750, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, 2H, J=7.5 Hz), 7.37 (t, 2H, J=7.5 Hz), 7.25 (t, 1H), 4.29-4.21 (m, 2H), 4.16 (q, 2H, J=7.2 Hz, OCH_2), 3.95-3.90 (m, 1H), 3.74 (m, 1H), 2.72-2.68 (m, 2H), 2.62-2.58 (m, 2H), 2.48-2.44 (m, 2H), 1.98-1.96 (m, 1H), 1.82-1.67 (m, 2H), 1.64-1.61 (m, 2H), 1.24 (t, 3H).

(±)-Ethyl *cis*-7-[3-(4-fluorophenyl)-4,5-trimethylene-pyrazol-1-yl]-3,5-di-hydroxyheptanoate (9ac)

Colorless oil (97%): IR (thin film) 3400, 2930, 1700, 1440, 1260, 1050, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.63 (m, 2H), 7.07-7.01 (m, 2H), 4.71 (br. s, 2 OH), 4.22-4.18 (m, 3H), 4.16 (q, 2H, J=6.9 Hz, OCH_2), 4.03-3.93 (m, 1H), 2.85-2.80 (m, 2H), 2.73-2.69 (m, 2H), 2.66-2.62 (m, 2H), 2.49-2.44 (m, 2H), 2.08-1.94 (m, 1H), 1.93-1.85 (m, 1H), 1.70-1.58 (m, 2H), 1.24 (t, 3H).

(±)-Ethyl *cis*-7-(3-phenyl-4,5-tetramethylenepyrazol-1-yl)-3,5-dihydroxyheptanoate (9bb)

Colorless oil (98%): IR (thin film) 3400, 2900, 1700, 1440, 1140, 1060, 760, 730 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, 2H, J=7.5 Hz), 7.37 (t, 2H), 7.25 (t, 1H), 4.29-4.21 (m, 2H), 4.17 (q, 2H, J= 5.5 Hz, OCH_2), 3.96-3.85 (m, 1H), 3.74-3.70 (m, 1H), 2.72-2.67 (m, 2H), 2.63-2.54 (m, 2H), 2.48-2.43 (m, 2H), 1.98-1.96 (m, 1H), 1.87-1.82 (m, 3H), 1.79-1.72 (m, 2H), 1.67-1.60 (m, 2H), 1.24 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2, 147.4, 139.8, 134.5, 128. 4, 127.1, 126.7, 113.7, 69.4, 68.6, 60.6, 45.1, 42.4, 41.9, 37.5, 23.3, 22.34, 22.31, 21.6, 14.1.

(±)-Ethyl *cis*-7-[3-(4-fluorophenyl)-4,5-tetramethylene-pyrazol-1-yl]-3,5-dihydroxyheptanoate (9bc)

Colorless oil (95%): IR (thin film) 3400, 2920, 1720, 1440, 1220, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66-7.59 (m, 2H), 7.08-7.02 (m, 2H), 5.65 (br. s, 2H, OH), 4.32 (m, 1H), 4.22-4.08 (m, 2H), 4.17 (q, 2H, J=7.1 Hz, OCH_2), 3.97 (m, 1H), 2.72-2.59 (m, 6H), 2.15-2.04 (m, 2H), 1.91-1.76 (m, 6H), 1.24 (t, 3H).

(±)-Ethyl *cis*-7-(3-phenyl-4,5-pentamethylenepyrazol-1-yl)-3,5-dihydroxyheptanoate (9cb)

Colorless oil (96%): IR (thin film) 3500, 2900, 1700, 1450, 1250, 1140, 1080, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49 (dd, 2H, J=7.4, 1.5 Hz), 7.38 (td, 2H, J=7.4, 2.4 Hz), 7.30 (td, 1H), 4.31-4.21 (m, 3H), 4.13 (q, 2H, J=7.2 Hz, OCH_2), 3.90-3.82 (m, 1H), 2.78-2.73 (m, 2H), 2.70-2.66 (m, 2H), 2.48-2.43 (m, 2H), 1.89-1.81 (m, 4H), 1.78-1.73 (m, 2H), 1.71-1.65 (m, 2H), 1.61-1.57 (m, 2H), 1.24 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2, 148.8, 143.2, 133.9, 128.6, 128.4, 127.2, 118.4, 69.2, 68.6, 60.5, 45.5, 42.3, 41.9, 37.9, 31.6, 28.4, 26.7, 26.1, 24.7, 14.1.

(±)-Ethyl *cis*-7-[3-(4-fluorophenyl)-4,5-pentamethylenepyrazol-1-yl]-3,5-dihydroxyheptanoate (9cc)

Colorless oil (96%): IR (thin film) ν 3400, 2920, 1710, 1440, 1220, 1060, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (dd, 2H, J=8.7, 2.0 Hz, $H_{2'}$ & $H_{6'}$), 7.07 (dd, 2H, $H_{3'}$ & $H_{5'}$), 4.31-4.18 (m, 2H), 4.15 (q, 2H, J=7.2 Hz, OCH_2), 4.05 (m, 1H), 3.88-3.79 (m, 1H), 2.82-2.73 (m, 2H), 2.68-2.56 (m, 2H), 2.50-2.44 (m, 2H), 1.90-1.80 (m, 4H), 1.78-1.56 (m, 6H), 1.25 (t, 3H).

(±)-Ethyl *cis*-7-(3-phenyl-4,5-hexamethylenepyrazol-yl)-3,5-dihydroxyheptanoate (9db)

Colorless oil (89%): IR (thin film) 3500-3100, 3040, 2910, 1700, 1400, 1260, 1030, 890, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57 (dd, 2H, J=7.3, 2.0 Hz), 7.42-7.26 (m, 3H), 4.32-4.23 (m, 3H, H_3 and H_7), 4.21-4.11 (m, 3H, -OCH_2- and H_5), 3.87 (s, 1H), 2.77 (t, 2H, J=6.3 Hz), 2.68 (t, 2H, J=6.3 Hz), 2.49-2.39 (m, 2H), 1.99-1.96 (m, 1H), 1.88-1.83 (m, 1H), 1.71 (m, 4H), 1.62 (m, 2H), 1.59 (m, 4H), 1.25 (t, 3H, J= 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2, 148.5, 141.5, 133.9, 128.3, 127.8, 127.3, 116.1, 69.5, 68.7, 60.6, 45.4, 42.3, 41.9, 37.9, 30.7, 28.3, 25.9, 25.5, 22.9, 22.7, 14.1.

(±)-Ethyl *cis*-7-[3-(4-fluorophenyl)-4,5-hexamethylenepyrazol-yl]-3,5-dhydroxyheptanoate (9dc)

Colorless oil (92%): IR (thin film) 3600-3000, 2920, 1700, 1520, 1490, 1360, 1300, 1220, 1090, 900, 830, 720, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53 (dd, 2H, J=8.7, 2.0 Hz), 7.07 (dd, 2H, J=8.7, 2.1 Hz), 4.32-4.24 (m, 3H, H_3 and H_7), 4.22-4.11 (m, 3H, -OCH_2- and H_5), 3.87 (m, 1H), 2.76 (t, 2H, J=6.1 Hz) 2.64 (t, 2H, J=6.1 Hz), 2.45-2.39 (m, 2H), 1.99 (m, 1H), 1.87 (m, 1H), 1.71-1.59 (m, 6H), 1.50 (m, 4H), 1.25 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2, 162.3 (d, $^2J_{C-F}$=243 Hz), 147.6, 141.5, 130.0 (d, $^4J_{C-F}$=3 Hz), 129.4 (d, $^3J_{C-F}$=7.8 Hz), 115.9, 115.2 (d, $^2J_{C-F}$=22 Hz), 69.4, 68.6, 60.6, 45.3, 42.3, 41.8, 37.9, 30.6, 28.2, 25.8, 25.4, 22.9, 22.6, 14.1.

***cis*-(±)-7-(3-Phenyl-4,5-trimethylenepyrazol-1-yl)-3,5-dihydroxyheptanoic acid (10ab)**

White solid (94%), mp 114-115°C: IR (KBr) 3400, 2900, 1680, 1440, 1310, 1250, 1060, 760, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, 2H, J=7.3 Hz), 7.38 (t, 2H, J=7.3 Hz), 7.27 (t, 1H), 5.90 (br. s, 2 OH), 4.28-4.12 (m, 3H), 4.03-3.94 (m, 1H), 2.86-2.82 (m, 2H), 2.72-2.65 (m, 2H), 2.63-2.58 (m, 2H), 2.48 (d, 2H, J=7.2 Hz), 1.98-1.86 (m, 2H), 1.71-1.60 (m, 2H).

***cis*-(±)-7-[3-(4-Fluorophenyl)-4,5-trimethylenepyrazol-1-yl]-3,5-dihydroxyheptanoic acid (10ac)**

White solid (98%), mp 118-120°C: IR (KBr) 3400, 2900, 1710, 1450, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65-7.60 (m, 2H), 7.07-7.01 (m, 2H), 5.94 (br. s, 2 OH), 4.19-4.12 (m, 3H), 4.02-3.96 (m, 1H), 2.83-2.78 (m, 2H), 2.72-2.67 (m, 2H), 2.65-2.58 (m, 2H), 2.48 (d, 2H, J=5.7 Hz), 2.04-1.82 (m, 2H), 1.78-1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 174.6, 162.2 (d, $C_{4'}$, $^1J_{C-F}$=246 Hz), 151.9, 143.4, 130.5, 127.3 (d, $C_{2' \& 6'}$, $^3J_{C-F}$=8 Hz), 123.7, 115.4 (d, $C_{3' \& 5'}$, $^2J_{C-F}$=22 Hz), 69.4, 68.3, 47.0, 42.1, 41.5, 37.4, 30.8, 24.4, 23.3.

***cis*-(±)-7-(3-Phenyl-4,5-tetramethylenepyrazol-1-yl)-3,5-dihydroxyheptanoic acid (10bb)**

White solid (95%), mp 121-122°C: IR (KBr) 3420, 2900, 1680, 1430, 1300, 1250, 1060, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (dd, 2H, J=8.4, 1.3 Hz), 7.36 (t, 2H, J=7.5 Hz), 7.27 (t, 1H), 6.30 (br. s, 2 OH), 4.26-4.17 (m, 2H), 4.15-4.05 (m, 1H), 3.98-3.88 (m, 1H), 2.70-2.66 (m, 2H), 2.61-2.57 (m, 2H), 2.48 (d, 2H, J=5.6 Hz), 1.88-1.73 (m, 6H), 1.65-2.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 174.5, 147.4, 140.0, 133.7, 128.5, 127.3, 126.9, 113.8, 69.6, 68.4, 45.2, 42.2, 41.6, 37.3, 23.2, 22.3, 22.2, 21.5; Mass spectrum, m/e (rel. intensity) 359 (1.3, M+1), 358 (6, M), 339 (25), 321 (55), 225 (21), 210 (94), 197 (52), 169 (15), 118 (23), 95 (21), 87 (100).

***cis*-(±)-7-[3-(4-Fluorophenyl)-4,5-tetramethylenepyrazol-1-yl]-3,5-dihydroxyheptanoic acid (10bc)**

White solid (94%), mp 122-123°C: IR (KBr) 3400, 2900, 1705, 1440, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76-7.48 (m, 2H), 7.19-7.11 (m, 2H), 4.33-4.20 (m, 3H), 3.99-3.96 (m, 1H), 2.77-2.66 (m, 4H), 2.54 (d, 2H, J=6.7 Hz), 2.17-2.07 (m, 1H), 2.00-1.93 (m, 3H), 1.91-1.84 (m, 2H), 1.75-1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.5, 161.7 (d, $C_{4'}$, $^1J_{C-F}$=246 Hz), 145.9, 138.4, 130.4, 128.0 (d, $C_{2' \& 6'}$, $^3J_{C-F}$=8 Hz), 115.0 (d, $C_{3' \& 5'}$, $^2J_{C-F}$=21 Hz), 112.9, 69.0,

68.0, 44.9, 42.4, 41.6, 37.3, 23.0, 22.02, 21.99, 21.3; Mass spectrum, m/e (rel. intensity) 378 (7, M+2), 377 (17, M+1), 376 (20, M), 375 (15), 360 (19), 359 (67), 358 (76), 357 (88), 285 (24), 229 (68), 228 (100), 215 (25), 187 (11), 148 (10), 102 (15), 88 (38), 87 (48).

cis-(±)-7-(3-Phenyl-4,5-pentamethylenepyrazol-1-yl)-3,5-dihydroxyheptanoic acid (10cb)

White solid (98%), mp 65-67°C: IR (thin film) 3400, 2900, 1710, 1430, 1370, 1230, 1040, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, 2H, J=7.3 Hz), 7.37 (t, 2H, J=7.3 Hz), 7.32 (dd, 1H), 5.01 (br. s, 2 OH), 4.28-4.19 (m, 3H), 3.91-3.84 (m, 1H), 2.74-2.72 (m, 2H), 2.68-2.65 (m, 2H), 2.47-2.44 (m, 2H), 1.87-1.84 (m, 4H), 1.74-1.56 (m, 6H).

cis-(±)-7-[3-(4-Fluorophenyl)-4,5-pentamethylene-pyrazol-1-yl]-3,5-dihydroxyheptanoic acid (10cc)

White solid (98%), mp 169-170°C: IR (KBr) 3400, 2900, 1700, 1440, 1260, 1040, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.44 (m, 2H), 7.08-7.03 (m, 2H), 4.73-4.65 (m, 1H), 4.25-4.18 (m, 4H), 3.88-3.77 (m, 1H), 2.79-2.75 (m, 2H), 2.65-2.61 (m, 2H), 2.42 (d, 2H, J=6.9 Hz, H_2), 1.88-1.85 (m, 2H), 1.77-1.69 (m, 2H), 1.67-1.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 174.6, 162.4 (d, $C_{4'}$, $^1J_{C-F}$=246 Hz), 147.7, 143.5, 130.3, 130.0 (d, $C_{2'\ \&\ 6'}$, $^3J_{C-F}$=8 Hz), 118.4, 115.2 (d, $C_{3'\ \&\ 5'}$, $^2J_{C-F}$=21 Hz), 69.0, 68.3, 45.5, 42.2, 41.7, 37.9, 31.5, 28.3, 26.6, 26.0, 24.7.

cis-(±)-7-(3-Phenyl-4,5-hexamethylenepyrazol-1-yl)-3,5-dihydroxyheptanoic acid (10db)

Semisolid (97%). IR (thin film) 3500-3100, 3040, 2910, 1700, 1400, 1260, 1030, 890, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (dd, 2H, J=7.3, 1.5 Hz), 7.42-7.26 (m, 3H), 4.31-4.20 (m, 3H, H_3, H_7), 3.80 (m, 1H), 2.76 (t, 2H, J=6.3 Hz), 2.66 (t, 2H, J=6.3 Hz), 2.57 (d, 2H, J=6.7 Hz), 2.06-1.96 (m, 2H), 1.69-1.59 (m, 6H), 1.49 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 174.3, 148.9, 142.0, 133.3, 128.3, 127.7, 127.5, 116.3, 69.3, 68.4, 44.6, 42.1, 41.5, 37.8, 30.6, 28.1, 25.8, 25.4, 22.7, 22.5.

cis-(±)-7-[3-(4-Fluorophenyl)-4,5-hexamethylene-pyrazol-1-yl]-3,5-dihydroxyheptanoic acid (10dc)

White crystal (96%), mp 140-143°C: IR (KBr) 3600-3000, 2920, 1700, 1520, 1490, 1300, 1220, 1090, 900, 830, 720, 640 cm^{-1}; ^1H NMR ($CDCl_3$ and DMSO-d_6 300 MHz) δ 7.52 (dd, 2H, J=8.7, 2.0 Hz), 7.07 (dd, 2H, J=8.7, 2.1 Hz), 4.28-4.15 (m, 3H, H_3, H_7), 3.90-3.64 (m, 1H), 2.78 (t, 2H, J=6.1 Hz) 2.64 (t, 2H, J=6.1 Hz), 2.46 (d, 2H, J=4.9 Hz), 2.02-1.98 (m, 1H), 1.89-1.84 (m, 1H), 1.71-1.64 (m, 4H), 1.63-1.57 (m, 2H), 1.50-1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 174.0, 162.1 (d, $^1J_{C-F}$=242 Hz), 147.3, 141.4, 130.1 (d, $^4J_{C-F}$=3 Hz), 129.3 (d, $^3J_{C-F}$=7.8 Hz), 115.6, 115.1 (d, $^2J_{C-F}$=21 Hz), 69.1, 68.4, 45.3, 42.1, 41.5, 37.6, 30.5, 28.1, 25.7, 25.3, 22.7, 22.4.

(±)-*trans*-6-[2-(3-Phenyl-4,5-trimethylenepyrazol-1-yl) ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11ab)

White crystal (57%), mp 123-124°C: IR (KBr) 3400, 2900, 1700, 1440, 1250, 1050, 770, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68 (dd, 2H, J=7.3, 1.1 Hz, $H_{2'}$ & $H_{6'}$), 7.34 (t, 2H, J=7.3 Hz, $H_{3'}$ & $H_{5'}$), 7.22 (td, 1H, $H_{4'}$), 4.64 (dtd, 1H, J_{H6-H5A}=11.5, J_{H6-H7A}=8.8, J_{H6-H5B}=J_{H6-H7B}=2.7 Hz, H_6), 4.21 (quintet, 1H, J=3.8 Hz, H_4), 4.15 (t, 2H, J=6.9 Hz, H_8), 3.56 (br. s, OH), 2.81 (t, 2H, J=6.8 Hz, H_4/H_6 of cyclohexene ring), 2.69 (t, 2H, J=6.8 Hz, H_6/H_4 of cyclohexene ring), 2.59 (tt, 2H, H_5 of cyclohexene ring), 2.55 (AB quartet, 2H, H_3), 2.23 (dtd, 1H, J_{gem}=14.5, J_{H7B-H8}=6.9, J_{H7B-H6}=3.8 Hz, H_{7B}), 2.04 (dtd, 1H, J_{gem}=14.5, J_{H7A-H6}=8.8, J_{H7A-H8}=6.9 Hz, H_{7A}), 1.86 (dt, 1H, J_{gem}=14.3, J_{H5B-H4}=J_{H5B-H6}=2.2 Hz, H_{5B}), 1.61 (ddd, 1H, J_{gem}=14.3, J_{H5A-H6}=11.4, J_{H5A-H4}=3.0 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 151.8, 144.6, 133.9, 128.5, 127.1, 125.6, 124.1, 73.0, 62.1, 46.0, 38.5, 35.8, 30.9, 24.6, 23.5. Anal. Data: Calc. for $C_{19}H_{22}N_2O_3$-0.75H_2O: C, 67.16, H, 6.92, N, 8.25; Found: C, 67.08, H, 7.00, N, 8.27.

(±)-*trans*-6-[2-{3-(4-Fluorophenyl)-4,5-trimethylene-pyrazol-1-yl}ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one(11ac)

White crystal (53%), mp 134-135°C: IR (KBr) 3400, 2900, 1700, 1430, 1230, 1050, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (dd, 2H, J=8.7, 1.8 Hz, $H_{2'}$ & $H_{6'}$), 7.05 (dd, 2H, $H_{3'}$ & $H_{5'}$), 4.67 (ddt, 1H, J_{H6-H5A}=11.6, J_{H6-H7A}=8.8, J_{H6-H5B}=J_{H6-H7B}=3.7 Hz, H_6), 4.27 (quintet, 1H, J=3.9 Hz, H_4), 4.17 (t, 2H, J=7.1 Hz, H_8), 3.19 (br. s, OH), 2.81 (t, 2H, J=6.8 Hz, H_4/H_6 of cyclohexene ring), 2.70 (t, 2H, J=6.8 Hz, H_6/H_4 of cyclohexene ring), 2.59 (tt, 2H, J=6.8 Hz, H_5 of cyclohexene ring), 2.58 (AB quartet, 2H, H3), 2.25 (dtd, 1H, J_{gem}=14.3, J_{H7B-H8}=7.1, J_{H7B-H6}=3.8 Hz, H_{7B}), 2.08 (dtd, 1H, J_{gem}=14.3, J_{H7A-H6}=8.8, J_{H7A-H8}=7.1 Hz, H_{7A}), 1.91 (dt, 1H, J_{gem}=14.3, J_{H5B-H4}=J_{H5B-H6}=3.6 Hz, H_{5B}), 1.68 (ddd, 1H, J_{gem}=14.3, J_{H5A-H6}=11.3, J_{H5A-H4}=3.1 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.1, 162.1 (d, $C_{4'}$, $^1J_{C-F}$=246 Hz), 151.9, 143.8, 130.5, 127.3 (d, $C_{2'\ \&\ 6'}$, $^3J_{C-F}$=8 Hz), 123.8, 115.4 (d, $C_{3'\ \&\ 5'}$, $^2J_{C-F}$=22 Hz), 73.0, 62.3, 46.0, 38.6, 35.9 (two C's), 31.0, 24.6, 23.6. Anal. Calcd. for $C_{19}H_{21}N_2O_3F$-0.5H_2O: C, 64.59, H, 6.23, N, 7.93; Found: C, 64.64, H, 6.27, N, 7.95.

(±)-*trans*-6-[2-(3-Phenyl-4,5-tetramethylenepyrazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11bb)

White crystal (53%), mp 137-138°C: IR (KBr) 3400,

2900, 1700, 1430, 1230, 1050, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (dd, 2H, J=7.3, 1.3 Hz, $H_{2'}$ & $H_{6'}$), 7.34 (t, 2H, J=7.3 Hz, $H_{3'}$ & $H_{5'}$), 7.24 (td, 1H, $H_{4'}$), 4.67 (dtd, 1H, J_{H6-H5A}=11.5, J_{H6-H7A}=8.8, J_{H6-H5B}= J_{H6-H7B}=3.3 Hz, H_6), 4.21 (quintet, 1H, J=3.9 Hz, $H_{4'}$), 4.17 (t, 2H, J=6.9 Hz, H_8), 3.40 (br. s, OH), 2.69-2.54 (m, 6H, H_3, H_7 & H_4 of cyclohexene ring), 2.23 (dtd, 1H, J_{gem}=14.5, J_{H7B-H8}=6.9, J_{H7B-H6}=3.8 Hz, H_{7B}), 2.06 (dtd, 1H, J_{gem}=14.5, J_{H7A-H6}=8.8, J_{H7A-H8}=6.9 Hz, H_{7A}), 1.90-1.84 (m, 3H), 1.82-1.73 (m, 2H), 1.63 (ddd, 1H, J_{gem}=14.3, J_{H5A-H6}=11.4, J_{H5A-H4}=3.2 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.1, 147.8, 139.9, 134.3, 128.4, 127.1, 126.8, 113.9, 73.1, 62.2, 44.2, 39.5, 35.9, 35.8, 23.3, 22.4, 22.3, 21.6. Anal. Calcd. for $C_{20}H_{24}N_2O_3$-0.5H_2O: C, 68.77, H, 7.16, N, 8.02; Found: C, 68.83, H, 7.18, N, 8.06.

(±)-*trans*-6-[2-{3-(4-Fluorophenyl)-4,5-tetramethylenepyrazol-1-yl}ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11bc)

White crystal (36%), mp 154-155°C: IR (KBr) 3360, 2900, 1700, 1430, 1210, 1050, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (dd, 2H, J=8.7, 1.8 Hz, $H_{2'}$ & $H_{6'}$), 7.05 (dd, 2H, $H_{3'}$ & $H_{5'}$), 4.69 (ddt, 1H, J_{H6-H5A}= 11.6, J_{H6-H7A}=8.8, J_{H6-H5B}=J_{H6-H7B}=3.7 Hz, H_6), 4.25 (quintet, 1H, J=3.9 Hz, H_4), 4.17 (t, 2H, J=6.8 Hz, H_8), 3.16 (br. s, OH), 2.67-2.57 (m, 6H, H_3, H_7 & H_4 of cyclohexene ring), 2.28 (dtd, 1H, J_{gem}=15.0, J_{H7B-H8}=6.9, J_{H7B-H6}=3.7 Hz, H_{7B}), 2.08 (dtd, 1H, J_{gem}=15.0, J_{H7A-H6}= 8.8, J_{H7A-H8}=6.9 Hz, H_{7A}), 1.92 (dt, 1H, J_{gem}=14.3, J_{H5B-H4}= J_{H5B-H6}=2.2 Hz, H_{5B}), 1.89-1.83 (m, 2H), 1.77-1.71 (m, 2H), 1.67 (ddd, 1H, J_{gem}=14.3, J_{H5A-H6}=11.4, J_{H5A-H4}=3.2 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.0, 162.3 (d, $C_{4'}$, $^1J_{C-F}$=245 Hz), 146.9, 140.0, 130.6, 128.4 (d, $C_{2'\ \&\ 6'}$, $^3J_{C-F}$=8 Hz), 115.3 (d, $C_{3'\ \&\ 5'}$, $^2J_{C-F}$=22 Hz), 113.4, 73.1, 62.4, 44.2, 38.6, 36.0, 35.9, 23.3, 22.4, 22.2, 21.6; Mass spectrum, m/e (rel. intensity) 360 (15.0, M+ 2), 359 (47.5, M+1), 358 (98.0, M), 340 (37.5, M-H_2O), 286 (30), 269 (7.5), 244 (12.5), 229 (77.5), 216 (100), 201 (19), 188 (13), 174 (14), 94 (31), 67 (15), 55 (50). Anal. Calcd. for $C_{20}H_{23}N_2O_3F$-0.5H_2O: C, 65.54, H, 6.54, N, 7.63; Found: C, 65.60, H, 6.57, N, 7.65.

(±)-*trans*-6-[2-(3-Phenyl-4,5-pentamethylenepyrazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11cb)

White crystal (38%), mp 150-151°C: IR (KBr) 3400, 2900, 1700, 1430, 1240, 1050, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (dd, 2H, J=7.3, 1.3 Hz, $H_{2'}$ & $H_{6'}$), 7.34 (t, 2H, J=7.3 Hz, $H_{3'}$ & $H_{5'}$), 7.29 (td, 1H $H_{4'}$), 4.64 (dtd, 1H, J_{H6-H5A}=11.5, J_{H6-H7A}=8.8, J_{H6-H5B}=J_{H6-H7B}=3.0 Hz, H_6), 4.14 (quintet, 1H, J=3.9 Hz, $H_{4'}$), 4.23 (t, 2H, J=7.0 Hz, H_8), 3.92 (br. s, OH), 2.78-2.73 (m, 2H, H_8/H_4 of cycloheptene ring), 2.66-2.63 (m, 2H, H_4/H_8 of cycloheptene ring), 2.53 (AB quartet, 2H, H_3), 2.17 (dtd, 1H, J_{gem}=14.5, J_{H7B-H8}=7.0, J_{H7B-H6}=3.8 Hz, H_{7B}), 2.02 (dtd, 1H, J_{gem}=14.5, J_{H7A-H6}=8.8, J_{H7A-H8}= 7.0 Hz, H_{7A}), 1.86-1.76 (m, 3H), 1.74-1.69 (m, 3H), 1.63 (ddd, 1H, J_{gem}=14.3, J_{H5A-H6}=11.3, J_{H5A-H4}=3.1 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 149.2, 143.3, 134.1, 128.5, 128.2, 127.3, 118.4, 73.2, 62.0, 44.7, 38.5, 36.3, 35.9, 31.6, 28.4, 26.7, 26.0, 24.7. Anal. Calcd. for $C_{21}H_{26}N_2O_3$-0.75H_2O: C, 68.57, H, 7.48, N, 7.62; Found: C, 68.60, H, 7.51, N, 7.59.

(±)-*trans*-6-[2-{3-(4-Fluorophenyl)-4,5-pentamethylenepyrazol-1-yl}ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11cc)

White crystal (78%), mp 168-169°C: IR (KBr) 3350, 2900, 1700, 1430, 1220, 1050, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44 (dd, 2H, J=8.7, 2.0 Hz, $H_{2'}$ & $H_{6'}$), 7.07 (dd, 2H, J=8.7, 1.9 Hz, $H_{3'}$ & $H_{5'}$), 4.71-4.63 (ddt, 1H, J_{H6-H5A}=11.3, J_{H6-H7A}=8.8, J_{H6-H5B} & H_{7B}= 3.4 Hz, H_6), 4.24 (t, 2H, J=7.0 Hz, H_8), 4.20 (quintet, 1H, J=3.9 Hz, H_4), 3.82 (br. s, OH), 2.76 (dd, 2H, J= 6.7, 4.5 Hz, H_4/H_8 of cycloheptene ring), 2.65-2.59 (m, 2H, H_8/H_4 of cycloheptene ring), 2.58 (AB quartet, 2H, H_3), 2.17 (dtd, 1H, J_{gem}=14.3, J_{H7B-H8}=8.8, J_{H7B-H6}= 3.8 Hz, H_{7B}), 2.03 (dtd, 1H, J_{gem}=14.3, J_{H7A-H6}=8.8, J_{H7A-H8} =3.8 Hz, H_{7A}), 1.88-1.61 (m, 6H, $H_{5,6,7}$ of cycloheptene ring), 1.89 (dt, 1H, J_{gem}=14.3, J_{H5B-H4}=J_{H5B-H6}=2.2 Hz, H_{5B}), 1.62 (ddd, 1H, J_{gem}=14.3, J_{H5A-H6}=11.3, J_{H5A-H4} =3.2 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 162.3 (d, $C_{4'}$, $^1J_{C-F}$=245 Hz), 148.3, 143.4, 130.1 (d, $C_{1'}$, $^4J_{C-F}$=3 Hz), 130.0 (d, $C_{2'\ \&\ 6'}$, $^3J_{C-F}$=8 Hz), 118.3, 115.2 (d, $C_{3'\ \&\ 5'}$, $^2J_{C-F}$=22 Hz), 73.1, 62.0, 44.7, 38.5, 36.4, 35.8, 31.6, 28.3, 26.7, 26.0, 24.7; Mass spectrum, m/e (rel. intensity) 374 (4, M+2), 373 (21, M+1), 372 (54, M), 354 (18, M-H_2O), 344 (19), 300 (48), 257 (38), 244 (58), 243 (100), 230 (58), 229 (30), 201 (15), 109 (18), 95 (18), 83 (18), 69 (27), 57 (30), 55 (42). Anal. Calcd. for $C_{21}H_{25}N_2O_3F$-0.5H_2O: C, 68.77, H, 6.82, N, 7.35; Found: C, 68.87, H, 6.85, N, 7.34.

trans-(±)-6-[2-(3-Phenyl-4,5-hexamethylenepyrazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11db)

White crystal (58%), mp 140-143°C: IR (KBr) 3500-3100, 3040, 2910, 1700, 1430, 1260, 1030, 890, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (dd, 2H, J=7.3, 1.5 Hz, $H_{2'}$ & $H_{6'}$), 7.40-7.26 (m, 3H), 4.78 (ddt, 1H, J_{H6-H5A}=11.4, J_{H6-H7A}=8.5, J_{H6-H5B}=J_{H6-H7B}=3.2 Hz, H6), 4.23-4.16 (m, 3H, OH and -NCH_2-), 4.12 (quintet, 1H, J=3.6 Hz, $H_{4'}$), 2.77 (t, 2H, J=6.1 Hz, H_4/H_9 of cyclooctene ring), 2.64 (t, 2H, J=5.8 Hz, H_8/H_4 of cyclooctene ring), 2.52 (AB quartet, 2H, J=4.5 Hz, H_3), 2.22 (dtd, 1H, J_{gem}=14.3, J_{H7B-H8}=8.7 Hz, J_{H7B-H6}=3.8 Hz, H_{7B}), 2.02 (dtd, J_{gem}=14.3, J_{H7A-H6}=8.8 Hz, J_{H7A-H8}=3.8 Hz, 1H, H_{7A}), 1.84 (d, 1H, J=14.3 Hz, H_{5B}) 1.69 (m, 4H), 1.59 (d, 1H, J=14.5 Hz, H_{5A}), 1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.4, 149.0, 141.5, 134.1,

128.3, 127.7, 127.3, 116.0, 73.3, 61.8, 44.5, 38.4, 36.2, 35.6, 28.1, 25.8, 25.3, 22.7, 22.5. Anal. Calcd. for $C_{22}H_{28}N_2O_3$-0.75H_2O: C, 69.21, H, 7.73, N, 7.34; Found: C, 69.24, H, 7.71, N, 7.35.

trans-(±)-6-{2-[3-(4-Fluorophenyl)-4,5-hexamethylenepyrazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (11dc)

White crystal (64%), mp 118-120°C: IR (KBr) 3600-3000, 2920, 1700, 1520, 1490, 1360, 1300, 1220, 1090, 900, 830, 720, 640 cm^{-1}; ^1H NMR ($CDCl_3$ and DMSO-d_6 300 MHz) δ 7.51 (dd, 2H, J=8.7, 2.0 Hz, $H_{2'}$ & $H_{6'}$), 7.07 (dd, 2H, J=8.7, 2.1 Hz, $H_{3'}$ & $H_{5'}$), 4.70 (ddt, 1H, $J_{H6\text{-}H5A}$=11.3, $J_{H6\text{-}H7A}$=8.8, $J_{H6\text{-}H5B\ \&\ H7B}$=3.4 Hz, H_6), 4.24-4.19 (m, 3H, H_4 and -NCH_2-), 3.87 (br. s, 1H, OH), 2.76 (t, 2H, J=6.0 Hz, H_4/H_9 of cyclooctene ring), 2.62-2.58 (m, 2H, H_9/H_4 of cyclooctene ring), 2.58 (AB quartet, 2H, H_3), 2.16 (dtd, 1H, J_{gem}=14.3, $J_{H7B\text{-}H8}$=8.7 Hz, $J_{H7B\text{-}H6}$=3.8 Hz, H_{7B}), 2.05 (dtd, J_{gem}=14.3, $J_{H7A\text{-}H6}$=8.8 Hz, $J_{H7A\text{-}H8}$=3.8 Hz, 1H, H_{7A}), 1.89 (dt, 1H, J_{gem}=14.3, $J_{H5B\text{-}H4}$=$J_{H5B\text{-}H6}$=2.6 Hz, H_{5B}), 1.62 (ddd, 1H, J_{gem}=14.3, $J_{H5A\text{-}H6}$=11.3 Hz, $J_{H5A\text{-}H4}$= 3.6 Hz, 1.68-1.59 (m, 4H), 1.50-1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.4, 162.3 (d, $^1J_{C\text{-}F}$=245 Hz), 148.1, 141.6, 130.3 (d, $^4J_{C\text{-}F}$=3 Hz), 129.6 (d, $^3J_{C\text{-}F}$ =7.8 Hz), 115.9, 115.2 (d, $^2J_{C\text{-}F}$=21 Hz), 73.3, 62.0, 44.5, 38.5, 36.3, 35.8, 30.6, 29.1, 25.6, 25.4, 22.8, 22.5. Anal. Calcd. for $C_{22}H_{27}N_2O_3F$-0.5H_2O: C, 66.84, H, 7.09, N, 7.09; Found: C, 67.04, H, 7.10, N: 7.09.

BIOLOGICAL ASSAY

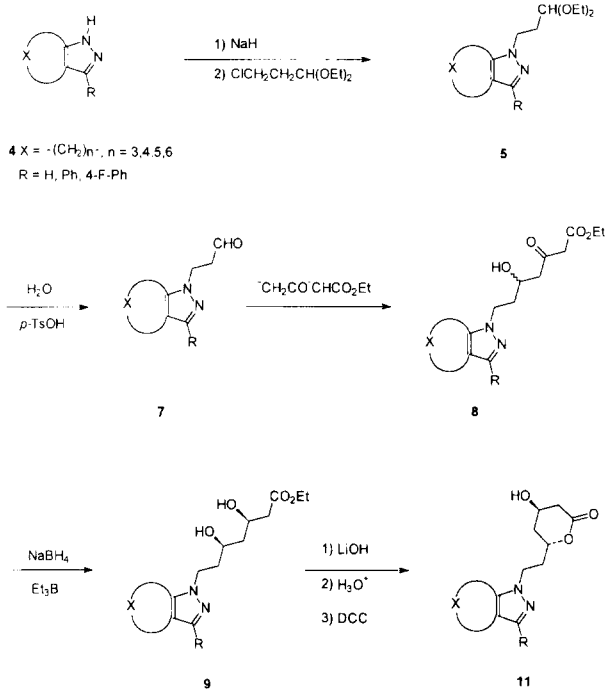
Rat Hepatic HMG-CoA Reductase Inhibition: Rat hepatic HMG-CoA reudctase activity is measured using a modification of the method previously described (Edwards and Lemongello, 1979). Rat hepatic microsomes are used as a source of enzyme, and the enzyme activity is determined by measuring the conversion of the ^{14}C-HMG-CoA substrate to [^{14}C]mevalonic acid. Livers are removed from 2-4 cholestyamine-fed, decapitated, Sprague-Dawley rats (220-250 g), and homogenized in phosphate buffer A. The homogenate is spun at 16000 g for 15 min at 4°C. The supernatent is removed and recentrifuged under the same conditions a second time. The second 16000 g supernatents is spun at 100000 g for 70 min at 4°C. Palleted microsomes are resuspended in a minimum volume of buffer A (3-5 mL/liver) and homogenized in a glass homogenizer. Dithiothreitol is added (10 mL), and the preparation is aliquoted, quick frozen in acetone/dry ice, and stored at -80°C. The specific activity of a typical microsomal preparation 0.68 nmol of mevalonic acid/mg of protein per min.. The reductase is assayed in 0.25 mL, which contains the following components at the indicated final concentrations: 0.04 M K_3PO_4, pH 7.2; 0.05 M KCl; 0.10 M sucrose; 0.03 M EDTA; 0.01 M dithiothreitol; 3.5 nM NaCl; 1% DMSO; 50-200 µg of microsomal protein; 100 µM of ^{14}C-[D,L]-HMG-CoA (0.05 µCi, 30-60 mCi/mmol); 2.7 mM NADPH. Reaction mixtures are incubated at 37°C. Under conditions described, enzyme activity increases linearly up to 300 µg of microsomal protein per action mixture and is linear with respect to incubation time up to 30 min. The standard incubation time chosen for drug studies is 20 min, which results in 12-15% conversion of HMG-CoA substrate to mevalonic acid product. [D,L]-HMG-CoA substrate is used as 100 µM, twice the concentration needed to saturate the enzyme under the conditions described. NADPH is used in excess at a level of 2.7 times the concentration required to achieve max. enzyme activity. Standardized assays for the evaluation of inhibitors are conducted according to the following procedure. Microsomal enzyme is incubated in the presence of NADPH at 37°C for 15 min. DMSO vehicle with or without test compound is added, the mixture further incubated for 15 min at 37°C. The enzyme assay is initiated by adding ^{14}C-HMG-CoA substrate. After 20 min of incubation at 37°C, the reaction is stopped by the addition of 25 µL of 33% KOH. [^3H]Mevalonic acid (0.05 µCi) is added, and the reaction mixture allowed to stand at rt for 30 min. Fifty microliters of 5 N HCl is added to lactonize the mevalonic acid. Bromophenol blue is added as a pH indicator to monitor an adequate drop in pH. Lactonization is allowed to proceed for 30 min at rt. Reaction mixtures are layered onto 2 g of AG 1-X8 anion exchange (Biorad, formate form), poured in 0.7 cm (i.d.) glass columns, and eluted with 2.5 mL of H_2O. The first 0.5 mL of eluent is discarded, and the next 2.0 mL is collected and counted for both tritium and carbon-14 in 10.0 mL of Opti-fluor (Packard) scincillation fluid. Results are calculated as nanomoles of mevalonic acid produced per 20 min and are are corrected 100% recovery of tritium. The effects of the compounds are expressed as IC_{50} values (concentration of drug producing 50% inhibition of enzyme activity) derived from composite dose response data from 4-6 experiments.

RESULTS AND DISCUSSION

Chemistry

The prerequisite 3-substituted 4,5-polymethylenepyrazoles were prepared in three steps from cycloalkanone by a modification of previously reported method (Ainsworth, 1963). Elaboration of pyrazole derivatives into designed compounds **11** was accomplished by employing previously reported synthetic sequence, shown in Scheme 1 (Jahng and Kim, 1995). The parent polymethylenepyrazoles and 3-substituted 4,5-polymethylenepyrazoles were reacted with 3-chlo-

ropropionaldehyde diethyl acetal (Büchi *et al.*, 1969) in the presence of NaH to yield N_1-alkylated products **5** and N_2-alkylated products **6** in good yields. This distribution of the alkylated products **5** and **6** is presumably due to the resonance of the deprotonated species. The ratios between **5** and **6** are highly dependent on the bulkiness of the substituent at C_3 as shown in Table I. The increased ratios of N_2-alkylated products in tetra- and pentamethylenepyrazoles may stem from the increased flexibility of the ring. These products can be readily separated, except the parent 4,5-polymethylenepyrazoles, and assigned to two isomeric partners by ^{1}H NMR spectra and NOE effect on H_ω by N-CH_2-(Jahng, 1996). Hydrolysis of acetal in the presence of *p*-TsOH afforded the corresponding aldehyde **7**, which was reacted with dianion, generated from ethyl acetoacetate, to lead hydroxyketo ester **8** in 69-98% of two-step yield. Aldol-type condensation of dianion with aldehyde, generated from acetals **6** was generally plagued with low yields and ardous procedures to isolate hydroxyketo ester products. Findings along with limitation of the amount of acetals **6** led to the discontinuation of synthetic studies on N_2-alkylated system (**6**). The keto group of **8** was, then, stereoselectively reduced by the previously reported method (Narasaka *et al.*, 1980 and 1984) (i. e. $NaBH_4$ in the presence of triethylborane) to yield *cis*-3,5-dihydroxy ester **9**. Over 98% of diasteroemric excess was observed in 300 MHz ^{1}H NMR spectrum of crude material thus confirming a high stereoselectivity of the reduction. Diasteromerically pure dihydroxy esters **9** were, then, hydrolyzed by treating with 3N LiOH, followed by acidification to give free acids (**10**) almost quantitatively. The free acids were then, lactonized by previously reported method (Kim and Jahng, 1995) or modification of such a method to afford **11** as final products.



Scheme 1.

Biological Activity

The racemic lactones were evaluated for their ability to inhibit partially purified rat liver HMG-CoA reductase *in vitro* and are summarized in Table II. With the increase of the ring size, the activities were slightly increased except hexamethylenepyrazole system. This result is somewhat consistent with previous data on a closely related system, wherein 7-(4-fluorophenyl)-4,5,6,7-tetrahydro-*2H*-indazol-3-yl group was employed as a hydrophobic anchor (Connolly, *et al.*, 1993, Kim, 1993). The most planar and rigid trimethylenepyrazole systems showed lower activity compared to their congeners reflecting that suitable conformational flexibility is required for the maximal interaction to the enzyme (Jahng, 1995). The decrease of activity in hexa-methylenepyrazole system implies that hexa- and pentametylene unit are the limit for the better interaction to the enzyme with respect to the spatial and conformatinal aspect. The compounds with 4-fluorophenyl substituents were more active than phenyl congeners.

In conclusion, compounds comprising a series of 6-{2-[3-(4-fluorophenyl)-4,5-polymethylenepyrazol-1-yl] ethyl}tetrahydro-4-hydroxy-2H-pyran-2-one were synthesized and tested for their ability to inhibit HMG-CoA reductase in a partially purified enzyme. The 3-substituted-4,5-polymethylenepyrazole nucleus, thus, can be a hydrophobic planar anchor for replacing dehydrodecalin moiety of mevinolin. Studies on the system with -CH=CH-(*trans*) bridge will be due in the near future.

Table I. Distributions of N_1-alkylated and N_2-alkylated products

R	X	N_1-Alkylated Product	N_2-alkylated Product
H	$-(CH_2)_3-$	55%	45%
CH_3	$-(CH_2)_3-$	60%	40%
Ph	$-(CH_2)_3-$	81%	19%
4-F-Ph	$-(CH_2)_3-$	85%	15%
H	$-(CH_2)_4-$	55%	45%
Ph	$-(CH_2)_4-$	77%	23%
4-F-Ph	$-(CH_2)_4-$	85%	15%
H	$-(CH_2)_5-$	55%	45%
Ph	$-(CH_2)_5-$	76%	24%
4-F-Ph	$-(CH_2)_5-$	70%	30%
H	$-(CH_2)_6-$	55%	45%
Ph	$-(CH_2)_6-$	80%	20%
4-F-Ph	$-(CH_2)_6-$	85%	15%

Table II. Physical Properties and *in vitro* HMG-CoA Reductase Inhibitory Activities of Lactones **11**

Compds	X	R	mp(°C)	molecular formula	IC_{50}[a],(μM)
11ab	$-(CH_2)_3-$	Ph	123-124	$C_{18}H_{22}N_2O_3$-0.75H_2O	0.22
11ac	$-(CH_2)_3-$	4-F-Ph	134-135	$C_{18}H_{21}N_2O_3F$-0.5H_2O	0.09
11bb	$-(CH_2)_4-$	Ph	137-138	$C_{20}H_{24}N_2O_3$-0.5H_2O	0.05
11bc	$-(CH_2)_4-$	4-F-Ph	154-155	$C_{20}H_{23}N_2O_3F$-0.5H_2O	0.02
11cb	$-(CH_2)_5-$	Ph	150-151	$C_{21}H_{28}N_2O_3$-0.75H_2O	0.03
11cc	$-(CH_2)_5-$	4-F-Ph	168-169	$C_{21}H_{25}N_2O_3F$-0.5H_2O	0.01
11db	$-(CH_2)_6-$	Ph	142-143	$C_{22}H_{28}N_2O_3$-0.75H_2O	0.05
11dc	$-(CH_2)_6-$	4-F-Ph	119-120	$C_{22}H_{27}N_2O_3F$-0.5H_2O	0.04
Mevinolin					0.04

[a]The values were obtained against HMG-CoA reductase (HMGR). The values shown represent the mean of 4-6 determinations.

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