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Synthesis and Biological Activity of Indazole-Derived HMG-CoA Reductase Inhibitors

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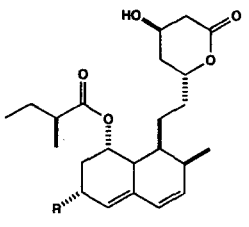
New hypolipaemic agents, in which substituted indazole nucleus is connected to tetrahydro-4-hydroxy-2H-pyran-2-one by a two-carbon bridge, were designed and synthesized to show significant inhibitory activity against microsomal HMG-CoA reductase in rat liver.

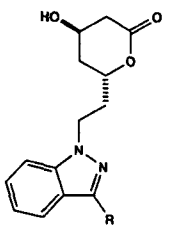
Key words : Hypolipaemic Agent, HMG-CoA reductase inhibitor, Substituted indazoles.

INTRODUCTION

One of the effective way to lower plasma cholesterol levels is to control *de novo* synthesis of cholesterol by selective inhibition of the biosynthetic step. Inhibition of the later steps, however, causes accumulation of sterol intermediates resulting serious adverse effects (Ariens, E. J., 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 compactin (**1a**) (Endo *et al.*, 1976; Brown *et al.*, 1976) and mevinolin (**1b**) (Endo, 1979; Alberts *et al.*, 1980) opened new era of 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 structure-activity relationship (SAR) studies upon these molecules as well as related compounds revealed that the chiral β-hydroxy-δ-lactone moiety or its equivalents is essential for the maximum activity (Stokker *et al.*, 1986; Jendralla *et al.*, 1991). The dehydrodecalin moiety of **1**, however, can be replaced by 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). We, herein, present the synthesis and preliminary biological activity of **2**, in which substituted indazole nucleus is connected to β-hydroxy-δ-lactone moiety by a two-carbon bridge.



1a R = H (Compactin)
b R = CH_3 (*Mevinolin*)



1a R = H
b R = *i*-Pr
c R = Ph
d R = 4-F-Ph

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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 ^1H NMR and 75.5 MHz for ^{13}C NMR) spectrometer and chemical shifts are reported in parts per million (ppm) downfield from 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 THF was obtained by distilling over Na and benzophenone ketyl and all other solvents were reagent grade and used directly without further purification. Substituted indazoles were prepared by literature method (Kim, *et al.*, 1995).

1-(3,3-diethoxypropyl)indazole (4a) and 2-(3,3-diethoxypropyl)indazole (5a)

To a suspension of 0.48 g (10 mmol) of 50% NaH in 10 mL of dry DMF was added a solution of 1.20 g (10 mmol) of indazole in 10 mL of DMF under N_2. When the gas evolution had ceased, 0.38 g (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 1.87 g of crude material, which was chromatographed on silica gel, eluting with *n*-hexane: EtOAc (1:1). The early fractions (Rf=0.48) afforded 1.00 g (41%) of 2-(3,3-diethoxypropyl)indazole (**5a**) as a pale yellow liquid: IR (thin film) 3040, 2960, 2920, 2870, 1610, 1440, 1420, 1370, 1120, 1060, 1020, 905, 825, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (s, H_3), 7.70 (d, J= 8.0 Hz, H_4), 7.42 (dm, J=9.0 Hz, H_7), 7.27-7.23 (m, H_5 & H_6), 4.46 (t, 2H, J=6.9 Hz, $=NCH_2CH_2$-), 4.40 (t, 1H, J=6.6 Hz), 3.60 (q, 2H, J=6.9 Hz, OCH_2CH_3), 3. 43 (q, 2H, J=6.9 Hz, OCH_2CH_3), 2.24 (dt, 2H, J=6.8, 5.7 Hz,=NCH_2CH_2CH=), 1.17 (t, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 139.5, 132.9, 126.0, 124. 0, 120.9, 120.3, 109.0, 100.6, 61.6, 44.5, 33.9, 15.2.

The latter fractions (R_f=0.25) afforded 1.38 g (54%) of 1-(3,3-diethoxypropyl)indazole (**4a**) as a pale yellow liquid: IR (thin film) 3040, 2960, 2880, 1610, 1440, 1420, 1370, 1120, 1060, 1020, 905, 825, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, H_3), 7.75 (dd, 1H, J=8.6, 0.9 Hz), 7.67 (dd, 1H, J=8.6, 0.9 Hz), 7.31 (td, 1H, J=7.0, 0.9 Hz), 7.10 (t, 1H, J=7.0 Hz), 4. 54 (t, 2H, J=7.1 Hz), 4.49 (t, 1H, J=5.6 Hz), 3.67 (q, 2H, J=7.1 Hz), 3.52 (q, 2H, J=7.1 Hz), 2.38 (dt, 2H, J =7.1, 5.6 Hz), 1.24 (t, 6H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 149.0, 125.7, 122.8, 121.7, 121.5, 120.0, 117.3, 100.4, 61.8, 49.5, 34.5, 15.2.

1-(3,3-Diethoxypropyl)-3-isopropylindazole (4b)

The same procedure described above in compound **4a** was employed for the preparation of **4b** to give **4b** as a colorless liquid (85%): IR (thin film) 3030, 2940, 2860, 1600, 1485, 1430, 1360, 1230, 1115, 870, 760, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.70 (d, 1H, J=8.0 Hz), 7.32 (t, 1H, J=8.0 Hz), 7.29 (t, 1H, J= 8.0 Hz), 7.04 (dd, 1H, J=8.0, 1.5 Hz), 4.38 (overlapped t, 3H, J=6.6 Hz), 3.61 (q, 2H, J=7.0 Hz), 3.42 (q, 2H, J=7.1 Hz), 4.41 (septet, 1H, J=7.0 Hz, -$CH(CH3)_2$, 2.20 (dt, 2H, J=7.0, 6.6 Hz), 1.43 (d, 6H, J=7.0 Hz, two CH_3), 1.17 (t, 6H, J=7.0 Hz, two CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ150.5, 140.8, 125.6, 121.5, 120. 6, 119.2, 108.9, 100.8, 61.4, 44.1, 33.8, 27.9, 22.2, 15.1.

1- (3,3-Diethoxypropyl)-3-phenylindazole (4c)

The same procedure described above in compound **4a** was employed for the preparation of **4c** to give **4c** as a pale yellow oil (86%): IR (thin film) 3020, 2920, 2850, 1600, 1470, 1405, 1365, 1115, 1050, 1005, 900, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96-7.90 (m, 3H), 7.52-7.44 (m, 3H), 7.43-7.35 (m, 2H), 7. 20-7.18 (m, 1H), 4.53 (overlapped t, 3H, J=6.9 Hz, $=NCH_2$ CH_2- and methine CH), 3.66 (q, J=6.9 Hz, OCH_2CH_3), 3.47 (q, OCH_2CH_3), 2.34 (q, J=6.8 Hz, $=NCH_2CH_2CH$=), 1.23 (t, J=6.9 Hz, 6H).

1-(3,3-Diethoxypropyl)-3-(4-fluorophenyl)indazole (4d)

The same procedure described above in compound **4a** was employed for the preparation of **4d** to give **4d** as a pale yellow oil (88%): IR (thin film) 3040, 2960, 2870, 1590, 1470, 1405, 1365, 1115, 1050, 1005, 945 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98-7.94 (m, 3H), 7.48-7.40 (m, 2H), 7.22-7.16 (m, 3H), 4.51 (overlapped t, 3H, J=6.9 Hz, $=NCH_2CH_2$- and methine CH), 3.67 (q, J=6.9 Hz, OCH_2CH_3), 3.48 (q, OCH_2CH_3), 2.32 (q, J=6.8 Hz, $=NCH_2CH_2CH$=), 1.22 (t, J=6.9 Hz, 6H).

3-(Indazol-1-yl)propanal (6a)

A solution of 0.50 g (2.0 mmol) of **4a** 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 0.30 g of crude material, which was chromatographed on silica gel, eluting with *n*-hexane: CH_2Cl_2 (2:3). The early fractions afforded 0.28 g (80%) of 3-(indazol-1-yl) propanal as a pale yellow liquid: IR (NaCl) ν 3040, 2920, 1700, 1610, 1415, 1380, 1300, 1165, 1055, 900, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 9.80 (t, 1H, J=0.9 Hz), 7.96 (s, 1H), 7.68 (d, 1H, J=8.4 Hz), 7.43 (dd, 1H, J=8.2, 0.7 Hz), 7.36 (td, 1H, J=7.0, 0.9 Hz), 7.12 (td, 1H, J=7.0, 0.9 Hz), 4.64 (t, 2H, J=6.5 Hz), 3.07 (t, 2H, J=6.5 Hz).

3-(3-Isopropylindazol-1-yl)propanal (6b)

The same procedure described above in compound **6a** was employed for the preparation of **6b** to give **6b** as a glassy oil (65%): IR (NaCl) 3040, 2940, 2860, 1700, 1600, 1480, 1360, 1290, 1220, 1150, 1080, 850, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 9.80 (t, 1H, J=0.9 Hz), 7.70 (d, 2H, J=8.0 Hz), 7.43 (dd, 1H, J=8.0, 0.7 Hz), 7.36 (td, 1H, J=7.0, 0.9 Hz), 7.08 (td, 1H, J=7.0, 0.9 Hz), 4.65 (t, 2H, J=6.5 Hz), 4.42 (septet, 1H, J=7.0 Hz), 3.09 (t, 2H, J=6.5 Hz), 1.44 (d, 6H).

3-(3-Phenylindazol-1-yl)propanal (6c)

The same procedure described above in compound **6a** was employed for the preparation of **6c** to give **6c** as a glassy oil (76%): IR (NaCl) 3020, 2920, 2810, 1700, 1600, 1465, 1375, 1260, 1150, 1055, 900,

730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, CHO), 7.90-7.85 (m, 3H), 7.50-7.43 (m, 3H), 7.43-7.34 (m, 2H), 7.18 (m, 1H), 4.61 (t, 2H, J=6.5 Hz), 3.08 (t, 2H, J=6.5 Hz).

3-[3-(4-Fluorophenyl)indazol-1-yl]propanal (6d)

The same procedure described above in compound **6a** was employed for the preparation of **6d** to give **6d** as white crystals (68%), mp 85.5-87°C: IR (NaCl) 3030, 2940, 2820, 1690, 1595, 1474, 1375, 1265, 1150, 1055, 945, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, CHO), 7.90-7.85 (m, 3H), 7.43-7.34 (m, 2H), 7.18-7.10 (m, 3H), 4.62 (t, 2H, J=6.5 Hz), 3.07 (t, 2H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.6 (d, C4', $^1J_{C-F}$=245 Hz), 142.8, 141.1, 130.0, 128.9 (d, C1', $^3J_{C-F}$=8 Hz), 126.1, 121.4, 120.9 (2 C's), 115.5 (d, C3' & 5', $^2J_{C-F}$=22 Hz), 109.3, 100.6, 61.6, 44.5, 33.9, 15.2.

(±)-Ethyl 7-(indazol-1-yl)-5-hydroxy-3-oxoheptanoate (7a)

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 THF solution containing 0.65 g (0.37 mmol) of **6a** 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 ether (3 x 50 mL). The combined organic layer was washed with H_2O, sat. $NaHCO_3$, and dried over anhyd. $MgSO_4$. Concentration under reduced pressure gave 0. 75g of crude material, which was chromatographed on silica gel, eluting with *n*-hexane: CH_2Cl_2 (3:2). The latter fractions gave 0.76g (72%) of pale yellow oil: IR (thin film) 3380, 2920, 1700, 1680, 1400, 1300, 1240, 1150, 1020, 905, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H, $H_{3'}$), 7.70 (d, 1H, J= 7.8 Hz, $H_{7'}$), 7.43 (d, 1H, J=7.8 Hz, $H_{4'}$), 7.36 (t, 1H, J=7.8 Hz, $H_{6'}$), 7.13 (t, 1H, $H_{5'}$), 4.60-4.49 (m, 2H, H_7), 4.14 (q, 2H, J=6.7 Hz, OCH_2CH_3), 4.05 (m, 1H, H_5), 3.96 (br. s, OH), 3.41 (s, 2H, H_2), 2.65 (m, 2H, H_4), 2.15-1.92 (m, 2H, H_6), 1.23 (t, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 203.0, 166.8, 140.6, 133.1, 126.4, 123.5, 121.9, 128.6, 109.2, 64.9, 61.3, 49.8, 49.6, 44.8, 36.2, 14.0.

(±)-Ethyl 7-(3-isopropylindazol-1-yl)-5-hydroxy-3-oxoheptanoate (7b)

The same procedure described above in compound **7a** was employed for the preparation of **7b** to give **7b** as a pale yellow oil (94%): IR (thin film) 3380, 2920, 1700, 1440, 1260, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 1H, J=8.1 Hz), 7.35 (m, 2H), 7.09 (m, 1H), 4.46 (m, 2H), 4.16 (q, 2H, J=7.0 Hz), 4.01 (m, 1H), 3.44 (s, 2H), 3.39 (septet, 1H, J=7.0 Hz), 2.67 (m, 2H), 2.06 (m, 1H), 1.93 (m, 1H), 1.44 (d, 6H, J=7.0 Hz), 1.27 (t, 3H, J=7.0 Hz).

(±)-Ethyl 7-(3-phenylindazol-1-yl)-5-hydroxy-3-oxoheptanoate (7c)

The same procedure described above in compound **7a** was employed for the preparation of **7c** to give **7c** as a glassy oil (67%): IR (thin film) 3200, 2900, 1700, 1600, 1470, 1330, 1250, 1100, 1070, 980, 900, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91-8.00 (m, 3H), 7.45-7.50 (m, 3H), 7.37-7.42 (m, 2H), 7.19 (t, J= 8.2 Hz, 1H), 4.58 (m, 2H), 4.17 (q, 2H, J=7.0 Hz), 4.07 (m, 1H), 3.40 (s, 1H), 2.69 (m, 2H), 2.07 (m, 2H), 1.22 (t, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 202.9, 166.8, 144.1, 141.2, 133.5, 128.7, 127.9, 127.4, 126.5, 121.5, 121.4, 121.1, 109.4, 65.0, 61.4, 49.8, 49.5, 45.0, 36.2, 14.0.

(±)-Ethyl 7-[3-(4-fluorophenyl)indazol-1-yl]-5-hydroxy-3-oxoheptanoate (7d)

The same procedure described above in compound **7a** was employed for the preparation of **7d** to give **7d** as a pale yellow oil (64%): IR (thin film) 3380, 2920, 1720, 1600, 1470, 1300, 1220, 1150, 1020, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (m, 3H), 7.45 (m, 2H), 7.18 (m, 3H), 4.58 (m, 2H), 4.15 (q, 2H, J=7.0 Hz), 4.06 (m, 1H), 3.59 (s, 1H), 3.41 (s, 2H), 2.70 (m, 2H), 2.15 (m, 1H), 2.03 (m, 1H), 1.23 (t, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 203.0, 166.8, 162.7 (d, 1C, $C_{4'}$, $^1J_{C-F}$=246 Hz), 143.2, 141.2, 130.5, 129.1 (d, $C_{2'\ \&\ 6'}$, $^3J_{C-F}$=8 Hz), 126.5, 121.3, 121.2, 121.1, 115.8 (d, $C_{3'\ \&\ 5'}$, $^2J_{C-F}$=22 Hz), 109.4, 64.9, 61.4, 49.8, 49.5, 45.0, 36.1, 14.0.

(±)-Ethyl *cis*-7-(indazol-1-yl)-3,5-dihydroxyheptanoate (8a)

To a solution of 0.17 g (0.060 mmol) of **7a** in 20 mL of dry THF at 0°C under Ar atmosphere, was added 0.6 mL (0.060 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 be stirred at -78°C for an addi-

tional 1.5 h. The reaction mixture was, then, diluted with 100 mL of 1N HCl, followed by extractions with ether (3 x 50 mL). The combined organic layer was washed with H_2O, dried over $MgSO_4$, concentrated under reduced pressure to give 0.28 g of 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 0.18 g (46. 5%) of **8a** as a red oil: IR (thin film) 3500, 2960, 1700, 1600, 1530, 1410, 1350, 1320, 1250, 1140, 1080, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, $H_{2'}$), 7.70 (d, J=7.8 Hz, $H_{4'}$), 7.46 (d, J=7.8 Hz, $H_{7'}$), 7. 36 (t, J=7.8 Hz, $H_{6'}$), 7.13 (td, $H_{5'}$), 4.65-4.47 (m, 2H), 4.24-4.16 (m, 1H), 4.16 (q, J=6.7 Hz, 2H), 3.96 (br. m, 1H), 3.78 (m, 1H), 2.44-2.41 (m, 2H), 2.10-1.94 (m, 2H), 1.65-1.50 (m, 2H), 1.23 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.2, 139.5, 132.9, 126.4, 123.6, 121.0, 120.6, 109.1, 68.9, 68.7, 60.6, 45.0, 42.4, 41.7, 37.3, 14.0; Mass spectrum, m/e (rel. intensity) 307 (5, M+1), 306 (20, M), 261 (13), 189 (8), 175 (10), 145 (13), 132 (43), 131 (100), 118 (42), 84 (19), 57 (20), 43 (28).

(±)-*cis*-Ethyl 7-(3-isopropylindazol-1-yl)-3,5-dihydroxyheptanoate (8b)

The same procedure described above in compound **8a** was employed for the preparation of **8b** to give **8b** as a colorless oil (57%): IR (thin film) 3400, 2940, 1710, 1440, 1290, 1170, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 1H, J=7.9 Hz), 7.37 (m, 2H), 7. 09 (m, 1H), 4.63 (m, 1H), 4.48 (m, 2H), 4.17 (q, 2H, J=7.1 Hz), 4.13 (m, 1H), 3.43 (septet, 1H, J=7.0 Hz), 2.45 (m, 2H), 2.00 (m, 2H), 1.61 (m, 2H), 1.45 (d, 6H, J=7.0 Hz), 1.26 (t, 3H, J=7.1 Hz).

(±)-*cis*-Ethyl 7-(3-phenylindazol-1-yl)-3,5-dihydroxyheptanoate (8c)

The same procedure described above in compound **8a** was employed for the preparation of **8c** to give **8c** as a glassy oil (98%): IR (thin film) 3500, 2900, 1710, 1590, 1400, 1290, 1250, 1140, 1050, 900, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91-8.01 (m, 3H), 7.47-7.51 (m, 3H), 7.7.38-7.43 (m, 2H), 7.19 (t, J=8.2 Hz, 1H) 4.56 (m, 2H, H_7), 4.29 (m, 1H), 4.17 (q, 2H, J=7.1 Hz), 3.86 (m, 1H), 2,42 (m, 2H), 2.08 (m, 2H), 1.64 (m, 2H), 1.23 (t, 3H, J=7.1 Hz).

(±)-*cis*-Ethyl 7-[3-(4-fluorophenyl)indazol-1-yl]-3,5-dihydroxyheptanoate (8d)

The same procedure described above in compound **8a** was employed for the preparation of **8d** to give **8d** as a colorless oil (90%): IR (thin film) 3500, 2960, 1700, 1610, 1520, 1470, 1410, 1220, 1150, 1040, 840, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (m, 3H), 7.46 (m, 2H), 7.18 (m, 3H), 4.58 (m, 2H), 4.48 (s, 1H), 4.23 (m, 1H), 4.12 (q, 2H, J=7.1 Hz), 4.08 (s, 1H), 3.88 (m, 1H), 2,43 (m, 2H), 2.08 (m, 2H), 1.60 (m, 2H), 1.23 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.4, 162.2 (d, $C_{4'}$, $^1J_{C\text{-}F}$=246 Hz), 143.1, 141. 1, 130.4, 129.1 (d, $C_{2'}$ & 6', $^3J_{C\text{-}F}$=8 Hz), 126.6, 121.2, 121.1, 115.8 (d, $C_{3'}$ & 5', $^2J_{C\text{-}F}$=22 Hz), 109.6, 109.5, 69.3, 68.8, 60.8, 45.0, 42.2, 41.6, 37.3, 14.1.

(±)-*trans*-6-[2-(Indazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (2a)

To the solution containing 0.66 g (0.23 mmol) of **8a** 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 6N HCl (pH=3) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with saline, dried over $MgSO_4$. The removal of the solvent afforded 0.60 g (94%) of white solid, which was directly subjected to lactonization. To the solution of 0.60 g (0.22 mmol) of dried *cis*-7-(indazol-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 x 70 mL). The oily material was purified by column chromatography, eluting with CH_2Cl_2. The latter fractions afforded 0.21 g (37%) of the product as a colorless oil (57%): IR (thin film) 3400, 3040, 2900, 1710, 1610, 1450, 1420, 1370, 1150, 1030, 900, 830, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, $H_{2'}$), 7.69 (d, J= 7.8 Hz, $H_{4'}$), 7.48 (d, J=7.8 Hz, $H_{7'}$), 7.36 (t, J=7.8 Hz, $H_{6'}$), 7.13 (t, $H_{5'}$), 4.68-4.56 (m, 2H), 4.54-4.52 (m, 2H), 4.32-4.29 (m, 1H), 3.09 (br. s, 1H), 2.70-2.58 (m, 2H), 2.31-2.27 (m, 1H), 2.22-2.17 (m, 1H), 1.93-1.87 (m, 1H), 1.73-1.67 (td, J=10.8, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 139.7, 133.3, 126.6, 123.8, 121.0, 120.8, 109.0, 62.3, 44.4, 38.5, 35.8, 35.5; mass spectrum, m/e (rel. intensity) 261 (3.5, M+1), 260 (20, M), 242 (3.5, M-H_2O), 188 (30), 132 (25), 131 (100), 118 (39), 77 (22), 71 (21), 57 (41), 43 (45). Anal. Data: Calc. for $C_{14}H_{16}N_2O_3$: C: 64.60, H: 6.20, N: 10.76; Found: C: 64.64, H: 6.19, N: 10.74.

(±)-*trans*-6-[2-(3-Isopropylindazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (2b)

The same procedure described above in compound

2a was employed for the preparation of **2b** to give **2b** as a colorless oil (67%): IR (thin film) 3400, 2900, 1710, 1450, 1250, 1060, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, 1H, J=8.1 Hz), 7.42 (d, 1H, J=8.1 Hz), 7.35 (td, 1H, J=8.0, 1.0 Hz), 7.08 (td, 1H, J=7.0, 1.0 Hz), 4.71 (ddt, 1H, J=11.4, 8.8, 3.1 Hz, H_6), 4.52 (t, 2H, J=6.9 Hz, H_8), 4.34 (quintet, 1H, J=3.7 Hz, H_4), 3.38 (septet, 1H, J=7.0 Hz), 2.71 (dd, 1H, J=17.5, 5.0 Hz, H_3), 2.58 (ddd, dt, 1H, J=17.5, 3.7, 1.3 Hz, H_3), 2.22 (m, 2H), 2.05 (s, 1H), 1.92 (dt, 1H, J=14.4, 3.6 Hz, H_{5B}), 1.72 (ddd, J=14.4, 11.3, 3.3 Hz, H_{5A}), 1.44 (d, 6H, J=7.1 Hz). Anal. Data: Calc. for $C_{17}H_{22}N_2O_3$: C: 67.53, H: 7.33, N:9.26; Found: C: 67.52, H: 7.29, N: 9.20.

(±)-*trans*-6-[2-(3-Phenylindazol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one (2c)

The same procedure described above in compound **2a** was employed for the preparation of **2c** to give **2c** as white crystals (66%), mp 125-127°C: IR (thin film) ν 3400, 2900, 1700, 1590, 1340, 1250, 1060, 720, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.97 (m, 3H), 7.41-7.49 (m, 3H), 7.34-7.39 (m, 2H), 7.18 (t, J= 7.4 Hz, 1H), 4.67 (ddt, 1H, J=11.3, 8.8, 3.4 Hz, H_6), 4.57 (t, 2H, J=6.4 Hz, H_8), 4.20 (quintet, 1H, J=3.7 Hz, H_4), 2.93 (br. s, OH), 2.59 (dd, 1H, J=17.5, 4.6 Hz, H_3), 2.50 (ddd, 1H, J=17.5, 3.5, 1.1 Hz, H_3), 2.32 (ddd, 1H, J=14.5, 6.9, 3.7 Hz, H_{7B}), 2.17 (dtd, 1H, J= 14.5, 8.8, 6.9 Hz, H_{7A}), 1.85 (dt, 1H, J=14.4, 3.6 Hz, H_{5B}), 1.62 (ddd, 1H, J=14.4, 11.3, 3.1 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.3, 144.3, 141.2, 133.4, 128.7, 127.9, 126.6, 121.5, 121.21, 121.17, 109.3, 73.1, 62.2, 44.3, 38.4, 35.7, 35.5.

(±)-*trans*-6-{2-[3-(4-Fluorophenyl)indazol-1-yl]ethyl} tetrahydro-4-hydroxy-2H-pyran-2-one (2d)

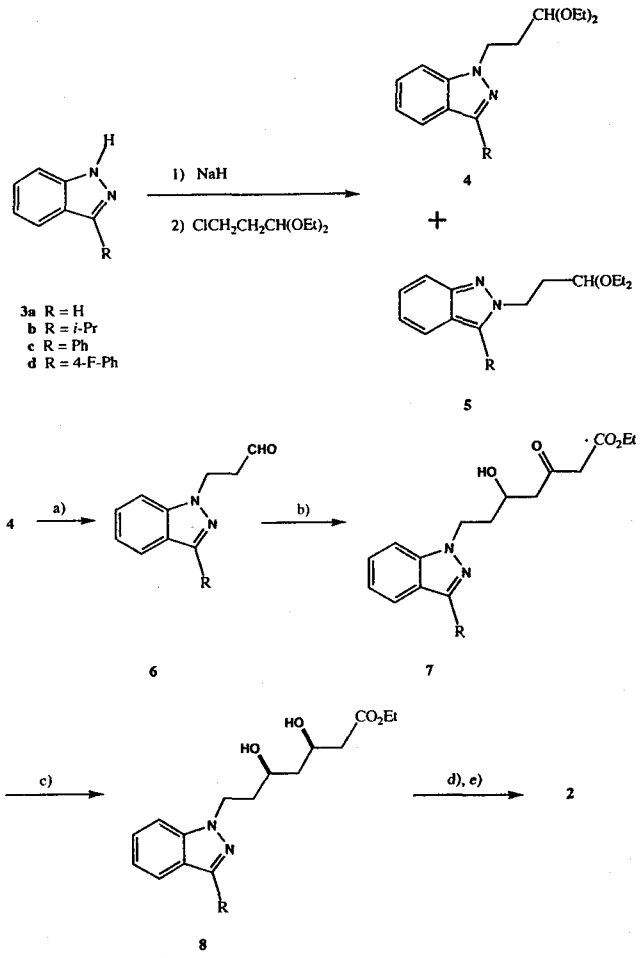
The same procedure described above in compound **2a** was employed for the preparation of **2d** to give **2d** as white crystals (56%), mp 145-147 °C: IR (thin film) υ 3400, 2900, 1700, 1470, 1210, 1040, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (m, 3H), 7.46 (m, 2H), 7.19 (m, 3H), 4.69 (ddt, 1H, J=11.4, 8.8, 3.2 Hz, H_6), 4.58 (t, 2H, J=6.9 Hz, H_8), 4.28 (quintet, 1H, J=3.7 Hz, H_4), 2.72 (s, 1H), 2.64 (dd, 1H, J=17.5, 4.6 Hz, H_3), 2.54 (ddd, 1H, J=17.5, 3.5, 1.1 Hz, H_3), 2.35 (ddd, 1H, J =14.5, 6.9, 3.7 Hz, H_{7B}), 2.20 (dtd, 1H, J=14.5, 8.8, 6.9 Hz, H_{7A}), 1.89 (dt, 1H, J=14.4, 3.6 Hz, H_{5B}), 1.68 (ddd, 1H, J=14.4, 11.3, 3.1 Hz, H_{5A}); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.2, 162.7 ((d, $C_{4'}$, $^1J_{C-F}$=245 Hz), 143.4, 141.3, 130.5, 129.1 (d, $C_{2'\&6'}$ $^3J_{C-F}$=8 Hz), 126.7, 121.33, 121.30, 121.0, 115.8 (d, $C_{c'\&5'}$ $^2J_{C-F}$=21 Hz), 109.4, 73.1, 62.4, 44.3, 38.5, 35.8, 35.6; mass spectrum, m/z (rel. intensity) 355 (5, M+1), 354 (25, M), 336 (6), 282 (12), 226 (18), 225 (100), 212 (32), 183 (8), 95 (7). Anal. Data: Calc. for $C_{20}H_{19}N_2O_3F$: C: 67.79, H: 5.40, N: 7.90; Found: C: 67.74, H: 5.37, N: 7.94.

Rat Hepatic HMG-CoA Reductase Inhibition:

Rat hepatic HMG-CoA reductase activity was measured using a modification of the literature method (Hulcher *et al.*, 1973).

RESULTS AND DISCUSSION

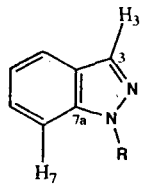
The synthetic sequence is quite straightforward as shown in Scheme 1. The prerequisite indazole and substituted indazoles were alkylated by 3-chloropropionaldehyde diethyl acetal (Buchi *et al.*, 1969). in the presence of NaH yielded N_1- and N_2-alkylated products **4** and **5** in 65:35 to 95:5 ratio. The portion of N_2-alkylated products is highly dependent on the bulkiness of the substituent at C_3. The ratios were 65: 35 where R is H, 78:22 where R is i-Pr, 95:5 where R is 4-F-Ph. This distribution of the alkylated products is presumably due to the resonance of the deprotonated

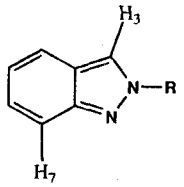


Key: a) H_2O, *p*-TsOH, b) $CH_2COCHCO_2Et$, c) $NaBH_4$, Et_3B, d) i) 1N, aq. LiOH, ii) H_3O^+, e) DCC, toluene.

Scheme 1.

Table I. ^1H and ^{13}C NMR Chemical Shifts for Seleceted Nuclei of Indazole and N-Substituted Indazoles.





R	H_3	C_3	H_7	C_{7a}
H	8.10[a]	133.4[b]	7.55[a]	139.9[b]
N_1-CH_3[a]	7.94	132.4	7.59	139.7
N_2-CH_3[a]	7.67	123.1	7.68	148.7
N_1-$CH_2CH_2CH(OEt)_2$[c]	7.98	132.9	7.42	139.5
N_2-$CH_2CH_2CH(OEt)_2$[c]	7.94	122.8	7.67	149.0

[a]Data from *J. Chem. Soc., Perkin Trans. 2,* 99 (1978); [b]Data from *J. Chem. Soc., Perkin Trans. 1.* 1695, (1975); [c]Data from from this work.

species. These products can be readily separated and assigned to two isomeric partners by ^1H NMR spectra and by comparing to the reported spectral data of 1- and 2-methylindazole (Palmer *et al.,* 1975, Fruchier *et al* 1977, and Begtrup *et al.,* 1978) and NOE effect on H_7 by N_1-CH_2-. Selected ^1H and ^{13}C resonances of indazole, N_1- and N_2-methyl indazoles and compounds **4a** and **5a** are shown in Table I.

In general, alkylation of indazole develops shielding effects on proton resonances and shifts upfield, most dramatically at the adjacent position of nitrogen (H_3) (Palmer, *et al,* 1975). In fact, methylation of indazole resulted in shileding effect on H_3 by 0.16 ppm upon N_1-methylation and by 0.43 ppm upon N_2-methylation. On the other hand, only N_2-methylation resulted downfield shift of H_7 by 0.13 ppm, presumably due to deshielding effect of the lone pairs of N_1. No significant shielding effects were observed upon for C_3 and C_{7a} ($\Delta\delta$=1.4 and 0.41 for C_3 and C_{7a}, respectively) upon N_1-methylation. N_2-Methylation, however, induced shielding effect on the ^{13}C resonance of C_3, thus shifted to upfield by 10.3 ppm. On the other hand, the ^{13}C resonance of C_{7a} was shifted to downfield by 8.8 ppm upon N_2-methylation. Therefore, the resonances of H_3, H_7, C_3 and C_{7a} of alkylated indazoles (**4** and **5**) could be a sensitive probe to determine each regioisomer. Similar deshielding effects ($\Delta\delta$=0.12 for H_7 and $\Delta\delta$=9.1 for C_{7a}) and shielding effects ($\Delta\delta$=0.16 for H_3 and $\Delta\delta$=10.6 for C_3), upon N_2-alkylation were observed in compound **5a** (Table I), which helped the assignment of each N_2-alkylated regioisomers, whose structure were additionally confirmed by measuring NOE effect (Jahng, 1995).

Hydrolysis of acetal afforded the corresponding aldehyde **6**, which was reacted with dianion, generated from ethyl acetoacetate, to lead hydroxyketo ester **8** in 52% of two-step yield. Aldol-type condensation of dianion with aldehyde, generated from acetals **5** was plagued with low yields and arduous procedures to isolate products, findings which led to the discontinuation of synthetic studies on N_2-alkylated system (**5**). The reason for this remained to be clarified. The keto group of **7** 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**. No diastereomeric isomer was observed in 300 MHz ^1H NMR spectrum, thus confirming a high stereoselectivity of the reduction. Dihydroxy esters **9** were, then, hydrolyzed by treating with 3N LiOH, followed by acidification to give free acids almost quantitatively. The free acids were not fully charaterized, but instead lactonized by known method in the presence of DCC to afford **2** as final products.

Table II. Effect of Mevinolin and Compounds **2** on the Activity of Microsomal HMG-CoA Reductase in Rat Liver.

Group	HMG-CoA reductase activitya)
Control	0.38±0.04
2a	0.27±0.03[b]
2b	0.22±0.02[b]
2c	0.20±0.03[b]
2d	0.19±0.03[b]
Mevinolin	0.24±0.03[b]

Rat were injected 25 mg/Kg of mevinolin or test compound p.o. daily for 10 days and sacrificed 24 hrs after the last dose. The values are the mean ± S.E.b) for 5 animals. a) n moles of CoA formed/min/mg protein. b) significantly different from control ($p<0.05$).

The inhibitory activity of these compounds on the microsomal HMG-CoA reductase in rat liver was evaluated by the method (Edwards *et al.,* 1979), described previously and the results are shown in Table 2. The compound **2d** is the most effective inhibitor of microsomal HMG-CoA reductase in rat liver, showing 20% activity increase compared to mevinolin.

In conclusion, substituted indazole nucleus can be a hydrophobic planar anchor for replacing dehydrodecalin moiety of mevinolin. Designed molecules, thus, can be a lead compound for potential hypolipaemic agents.

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