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Research Article

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Improved process for Centchroman, a selective estrogen receptor modulator (SERM)

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ABSTRACT

Centchroman (Ormeloxifene) is a non-steroidal SERM. This is used as an oral contraceptive and showed anti cancer activities also. It is synthesized in a five step high yielding process.

Keywords: Phenyl acetic acid, Iso propyl magnesium chloride, Resorcinol monomethyl ether, Phenol, 1-(2-chloro ethyl)-pyrrolidine.

INTRODUCTION

DL-Centchroman (INN: Ormeloxifene) [1,2] developed at central drug Research Institute (CDRI) Lucknow (India), is a non-steroidal, once-a-week oral contraceptive. It was introduced in India in 1992, and included in the National family welfare programme in 1995[3]. Its contraceptive action is quickly reversible. Recent studies have shown its potent anti-cancer activities in breast, head and neck, and chronic myeloid leukemia cells [4]. Even though l-isomer [5] found to posses twice the anti-fertility activity only dl-isomer is introduced in the market. The structure of the drug Centchroman (**Fig-1**) was unequivocally established by its X-ray crystal structure [6].

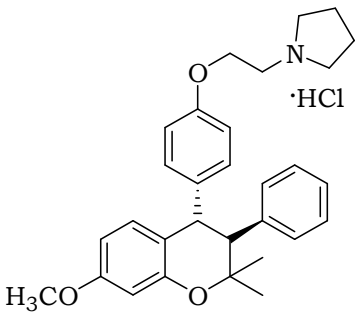
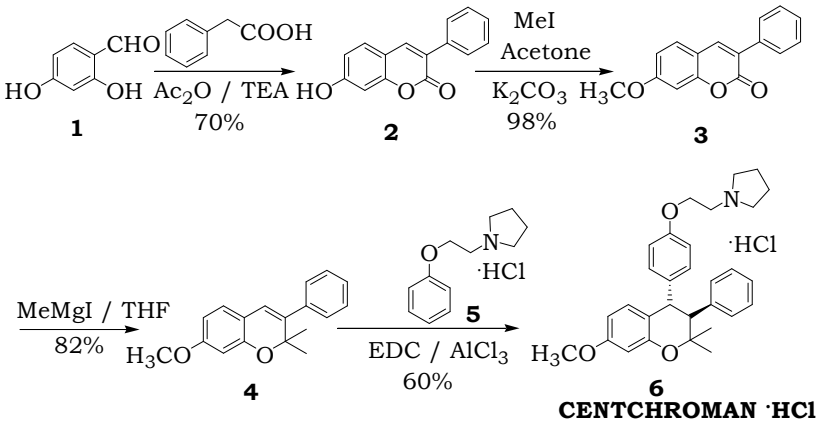


Fig-1: **CENTCHROMAN (ORMILOXIFENE) ·HCl.**

The synthesis of this drug as developed by CDRI [7] did not see much improvement over a period [8]. The latest [8b] process by CDRI team is described in **Scheme-I.**



Scheme-I: **CDRI Process of Centchroman hydrochloride**

The von Pechmann reaction of 2, 4-dihydroxy benzaldehyde with phenyl acetic acid gave 70% yield of compound **2**, which was alkylated with methyl iodide to give **3**. The chromene **3** was dimethylated to give compound **4**. Compound **4** when reacted with N-(Pyrrolidino) ethoxy benzene hydrochloride **5** gave the drug **6** in 60% yield. The overall yield according to this method is 30%. The purity of final compound is 99%, and the impurities were not detailed.

EXPERIMENTAL SECTION

Most of the reagents used in this work were obtained from commercial suppliers and were of LR/AR grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on POLMON melting points apparatus (Model-96) and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded by using a Bruker 400 Spectrometer with TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR Spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied Bio Systems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240CHN elemental analyzer. Analytical TLC was conducted on E-Merck 60F254 aluminium-packed plates of silica gel (0.2 mm). Developed plates were visualized by using UV light or in an iodine chamber. HPLC was performed by using a Shimadzu 2010 instrument.

Synthesis of 3-Methyl-2-phenyl-but-2-enoic acid (7) [9].

A solution of phenyl acetic acid (100g, 0.74 mol) in dry THF (1000 mL) was added to the solution of Iso propyl magnesium chloride in THF (750 mL, 1.5 mol, 2M, in 500 mL THF) at RT. The resulting thick solution was stirred at 40°C for 1 hr, then acetone (65 g, 1.12 mol) was added at RT over 30 min and stirred 40°C for 1 hr. After TLC showed the absence of starting material, it was quenched with 15% aq solution of H_2SO_4 (800 mL) under ice cooling (5-10°C), then stirred at RT for 30 min. The organic layer was separated and the aqueous phase was extracted with DCM (3X250 mL), and total organic phase was concentrated under vacuum, to get dark oil 150 g. (Hydroxy acid).

To the crude solution (150 g and 700 mL DCM) Conc.H_2SO_4 (180 mL) was added slowly at RT during 1.5 hr, and then stirred at RT for 1 hr. After TLC showed the completion of reaction, reaction mass was concentrated under vacuum to get yellow colored solution. This mass was poured in to ice water (3000 mL) slowly. The white precipitate was formed, stirred for 15 min and filtered off. The cake was washed with water (200 mL) and hexane (100 mL) and dried to get desired product **7**. Yield: 110.0 g (85.14%), description: Off white solid, melting point : 148-150.2°C, HPLC purity: 98.71%, IR (KBr, cm^{-1}): 2910, 1681, 1616, 1295, 942, 740; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 1.71 (3H, s, **CH$_3$**), 2.24 (3H, s, **CH$_3$**), 7.18 (2H, d, *J* = 7.14 Hz, Ar**H**), 7.37-7.29 (3H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 22.68, 23.0, 128.5, 129.64, 131.17, 138.69, 142.18, 169.93; Mass for $C_{11}H_{12}O_2$ [M+1] 176;

Synthesis of 7-Methoxy-2,2-dimethyl-3-phenyl-chroman-4-one (8).

To a stirred solution **7** acid (70 g, 0.4mol) and PPA (450 g) 3-methoxy phenol (73 g, 0.59 mol) added at RT and stirred at 60-65°C for 4 hr. Reaction completion was monitored by TLC, and after completion the reaction mass was

poured into ice water (2500 mL). Reaction mass was extracted with DCM (3X500 mL), and the combined organic extracts were washed with 5% $NaHCO_3$ solution (500mL) and 10% NaCl solution. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. A yellow colored solid appeared which was stirred at 15-20°C for 10 min in 150 mL methanol, to get desired product **8**. Yield: 75.0 g (67.5%), description: Yellow color solid, Melting point: 112.3-114.9°C; HPLC purity: 98.66%, IR (KBr, cm^{-1}): 2981, 1673, 1603, 1441, 1260, and 1130; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 1.30 (3H, s, **CH_3**), 1.49 (3H, s, **CH_3**), 3.64 (1H, s, CO-**CH**-Ar), 3.87 (3H, s **OCH_3**), 6.47 (1H, s, Ar**H**), 6.61 (1H, d, *J* = 8.57 Hz, Ar**H**), 7.20 (2H, d, *J* = 6.65 Hz, Ar**H**), 7.275 (3H, m, Ar**H**), 7.86 (1H, d, J = 8.73 Hz, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 24.53, 27.0, 55.6, 62.23, 81.98, 101.23, 109.78, 113.80, 127.54, 128.59, 129.17, 129.57, 135.52, 161.50, 166.42, 191.19; Mass for $C_{18}H_{18}O_3$ [M+1] 282.3; Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.70; H, 6.48;

Synthesis of 7-Methoxy-2,2-dimethyl-3-phenyl-2H-chromene (4) [8].

LAH (14.5 g, 0.38 mol) was taken in to a RB flask under nitrogen atmosphere and THF (200 mL) was added slowly for 15 min at RT (little exothermic). To this reaction mass **8** (70.0 g, 0.25 mol, dissolved in 500 mL THF) was added at RT over 1 hr and temperature of the reaction went up to reflux. It was stirred at reflux for 30 min. After completion of the reaction (monitored by TLC) reaction mass was cooled to 5-10°C and quenched the reaction mass by adding ethyl acetate (500 mL) slowly followed by aq ammonium chloride (500 mL) at 10-15°C over 1 hr. Reaction mass was filtered on hiflo bed and washed with ethyl acetate (200 mL). The filtrate was stirred for 30 min, separated the organic phase. The aq phase was extracted with ethyl acetate (2X250 mL), and the combined organic extracts were washed with brine solution (500 mL), and organic phase was dried over Na_2SO_4 and concentrated under vacuum to get crude product. Yield: 70.0 g (98%), HPLC purity: 89.6%, Description: Light yellow colored oil. It was taken as such for dehydration and purified at that stage.

Dehydration: To a stirred solution of alcohol (70.0 g, 0.18mol) in toluene (700 mL), PTSA (0.7 g) was added at RT and heated and stirred at 40-45°C for 1 h. Reaction was completed (monitored by TLC). The reaction mass was poured in to water (1000 mL), organic layer separated and then aq layer was extracted with ethyl acetate (2X250 mL). Organic extracts were combined and washed with 5% bicarbonate solution (250 mL), and 10% NaCl solution (250 mL). Organic layer was dried over sodium sulphate and concentrated under vacuum. Organic layer was co-distilled with methanol (200 mL). The obtained solid was stirred in methanol (100 mL) at 10-15°C for 15 min and filtered. Cake was washed with methanol (50 mL) to get desired product **4**. Yield: 50.0 g (72.2%), description: White color solid, melting point : 67.82-69.2°C; HPLC purity: 99.86%, IR (KBr, cm^{-1}): 2935, 1592, 1609, 1494, 1200, 1029, 844; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 1.55 (6H, s, 2X**CH_3**), 3.81 (3H, s, **OCH_3**), 6.30 (1H, s, Olefini**c CH**), 6.46 (2H, m, Ar**H**), 6.99 (1H, d, *J* = 8.612 Hz, Ar**H**), 7.33-7.34 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 26.13, 28.71, 55.32, 111.39, 113.48, 123.83, 124.93, 126.99, 127.70, 127.99, 128.45, 135.97, 136.61, 141.32, 158.7; Mass for $C_{18}H_{18}O_2$ [M+1] 266.

Synthesis of 4-(7-Methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl)-phenol (9) [5,7].

A solution of $AlCl_3$ (40 g, 0.3 mol) and phenol (25 g, 0.27 mol) in benzene: hexane (1:1, 1000 mL) stirred at RT for 30 min. A solution of 4 (70 g, 0.26 mol) and Phenol (35 g, 0.37 mol) in benzene: hexane (1:1, 1000 mL) mixture was added to the above stirred solution at 0-5°C for 2 h. The reaction mixture stirred further for 10 h. Reaction was completed (monitored by TLC). The reaction mixture mass was quenched by adding ice water (1500 mL) and con HCl (100 mL), the organic layer was separated and aq layer was extracted with ethyl acetate (3X250 mL). The combined extracts were washed with brine solution (500 mL) and dried over sodium sulphate and evaporated. To the obtained solid hexane (200 mL) was added and stirred for 15 min and filtered. The cake was re-crystallized from DMF (4 vol) and ethanol (10 vol) mixture two times, to obtain the desired product **9**. Yield: 55.0 g (57.7%), HPLC purity: 98.66%, Description: Off white solid, Melting point: 266.2-271.4°C; IR (KBr, cm^{-1}): 3398, 2984, 1614, 1502, 1266, 1098; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 1.23 (3H, s, **CH_3**), 1.37 (3H, s, **CH_3**), 3.17 (1H, d, *J* = 12.16 Hz, Ar-**CH**-Ar), 3.77 (3H, s, **OCH_3**), 4.32 (1H, d, *J* = 12.0 Hz, Ar-**CH**-Ar), 4.42 (1H, s, **OH**), 6.38 (1H, d, *J* = 8.42 Hz, Ar**H**), 6.43 (1H, s, Ar**H**), 6.56 (2H, d, *J* = 8.10 Hz, Ar**H**), 6.62 (1H, d, *J* = 8.60 Hz, Ar**H**), 6.84 (2H, d, *J* = 6.07 Hz, Ar**H**), 7.25-7.13 (5H, m, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 19.83, 28.55, 43.22, 55.84, 56.72, 101.08, 106.79, 114.85, 118.55, 126.32, 127.60, 129.66, 130.58, 133.94, 139.16, 153.70, 155.15, 158.68;

Synthesis of 1-{2-[4-(7-Methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl)-phenoxy]-ethyl}-pyrrolidine (Centchroman) Hydochloride [6].

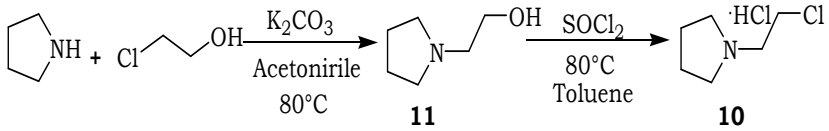
(60%) NaH (2.7 g, 0.069 mol) was taken in to a RB flask under nitrogen atmosphere and DMF (30 mL) was added drop wise for 5 min at RT. To this solution compound **9** (10 g, 0.027 mol in 50 mL DMF) was added over 20 min at

RT and stirred for 10 min. To the reaction mass 1-(2-Chloro ethyl) pyrrolidine (4.7 g, 0.027 mol, in 20 mL DMF) solution was added over 10 min at RT, reaction mass was stirred for 3 h at 60-65°C, and after completion of the reaction (monitored by TLC), 10 mL of methanol was added to the reaction mass at RT, and quenched into ice water solution (300 mL). The mass was extracted with ethyl acetate (3X200 mL). Organic extracts were combined and washed with NaCl solution (200 mL) and dried over sodium sulphate and concentrated under vacuum, to get crude product.

HCl Salt: Crude was diluted in diisopropyl ether (250 mL) and cooled to 5-10°C. HCl gas was passed for 15 min, and stirred for 15 min at RT. The reaction mass was concentrated completely and ethyl acetate (150 mL) was added and stirred for 30 min and the formed solid was filtered.

Purification: To the crude compound (10 g) ethyl acetate (150 mL) was added at RT and then raised to 75-80°C, and stirred for 30min., clear solution formed. It was cooled to RT and stirred for 15 min and filtered. The Cake was washed with ethyl acetate (25 mL), to get Centchroman hydrochloride. Yield: 8.5 g (64%), HPLC purity: 99.94%, Description: Off white solid, Melting point: 168-171°C; IR (KBr, cm^{-1}): 3420, 2972, 1617, 1504; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 1.16 (3H, s, **CH_3**), 1.26 (3H, s, **CH_3**), 1.85 (2H, m, N-CH_2-**CH_2**), 1.97 (2H, m, N-CH_2-**CH_2**), 3.06 (2H, m, OCH_2-**CH_2**), 3.30 (1H, d, *J* = 12.4 Hz, Ar-**CH**-Ar), 3.53 (4H, m, **CH_2**-N-**CH_2**), 3.68 (3H, s, **OCH_3**), 4.20 (2H, m, **OCH_2**), 4.53 (1H, d, *J* = 12.2 Hz, Ar-**CH**-Ar), 6.32-6.43 (3H, m, Ar**H**), 6.75 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.03 (2H, d, *J* = 8.28 Hz, Ar**H**), 7.13 (1H, t, *J* = 7.18 Hz, Ar**H**), 7.21 (2H, t, *J* = 7.18 Hz, Ar**H**), 7.30 (2H, m, Ar**H**), 10.70 (1H, s, brs, **H**Cl); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 20.13, 23.16, 28.77, 43.95, 53.86, 54.28, 55.24, 57.49, 63.28, 78.20, 101.44, 107.51, 114.0, 118.31, 126.81, 128.0, 130.27, 130.87, 137.46, 139.20, 154.16, 155.5, 159.24;

Intermediate preparation:



Synthesis of 2-Pyrrolidin-1-yl-ethanol from pyrrolidine (11) [10,11].

To a stirred solution of pyrrolidine (20 g, 0.28 mol) and potassium carbonate (38 g, 0.28 mol) in acetonitrile (300 mL) 2-chloro ethanol (22.5 g, 0.28 mol in 100 mL acetonitrile) was added at 75-80°C for 45 min, stirred for 16 h, and after completion of the reaction (monitored by TLC), reaction mass was cooled to RT, filtered the solids and organic layer was concentrated completely, to get dark oil . It was distilled under reduced pressure, to get color less oil. Yield: 16.5 g (51%), Description: color less oil. IR (KBr, cm^{-1}): 3377, 1659, 1461, 1058; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 1.74 (4H, m, N-CH_2-**CH_2**-**CH_2**), 2.50 (4H, m, **CH_2**-N-**CH_2**), 2.58 (2H, t, *J* = 5.55 Hz, OCH_2-**CH_2-N**), 3.59 (2H, t, *J* = 5.59 Hz, HO**CH_2**-CH_2), 4.10 (s, 1H, **OH**). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 23.29, 53.99, 58.11, 60.04;

Synthesis of 1-(2-Chloro-ethyl)-pyrrolidine hydro chloride (10) [10,11].

To a stirred solution of 2-pyrrolidine-1-yl ethanol (10 g, 0.08 mol) and toluene (100 mL) thionyl chloride (11.1 g, 0.13 mol) was added drop wise at 0-5°C for 15 min, and stirred at 75-80° For 4 h, and after completion of the reaction (monitored by TLC) reaction mass was cooled to RT and concentrated under vacuum. Diisopropyl ether (150 mL) was added and stirred for 15 min. The obtained product was filtered and washed with diisopropyl ether (5X100 mL). Yield: 11.0 g (95%), Description: light yellow color solid, Melting point : 165-167°C, IR (KBr, cm^{-1}): 3430, 2935, 2588, 2480, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): δ = 2.15 (4H, m, N-CH_2-**CH_2**-**CH_2**), 2.97 (2H, m, **CH_2**-N), 3.50 (2H, m, N-**CH_2**), 3.80 (2H, m, Cl-CH_2-**CH_2**), 4.01 (2H, t, *J* = 6.36 Hz, Cl-**CH_2**-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 2.309, 37.98, 54.17, 55.59.

RESULT AND DISCUSSION

Retro synthetic analysis of Centchroman hydrochloride leads to phenyl acetic acid and resorcinol monomethyl ether as starting materials as shown in **Fig 2**.

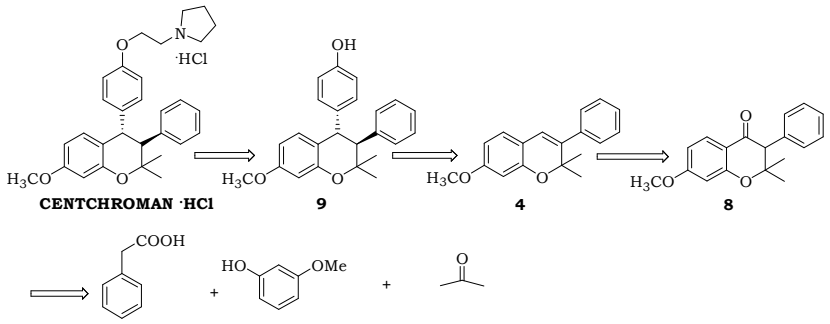
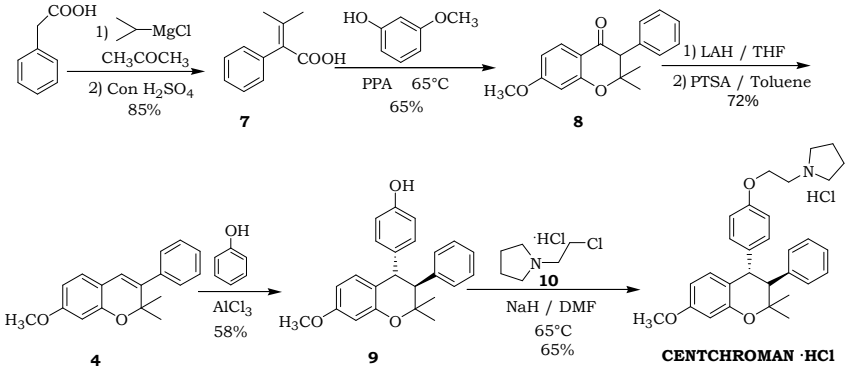


Figure 2. Retro synthetic analysis of Centchroman hydrochloride

In the synthesis of Centchroman hydrochloride, the first critical intermediate 7-methoxy-2,2-dimethyl-3-phenyl-2H-chromene(**4**) [8] was prepared in a different way with good yields. The starting material phenyl acetic acid was reacted with acetone in the presence of Iso propyl magnesium chloride (2M) in THF at 40°C gave 3-Methyl-2-phenyl-but-2-enoic acid (**7**) [9]. Acid **7** was condensed with resorcinol mono methyl ether in the presence of PPA at 65°C gave 7-Methoxy-2,2-dimethyl-3-phenyl-chroman-4-one (**8**). Keto compound **8** was reduced with lithium aluminum hydride (LAH) followed by dehydration in toluene gave critical intermediate **4** in good yields**.**

The one step synthesis of drug from **4** did not work well (poor yield vs 60%-CDRI) in our hands. During the first step of alkylation of **4** with phenol in the presence of aluminum chloride obtained 4-(7-Methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl)-phenol (**9**). We did observe the cis compound of **9** (~10%) in this reaction. It was eliminated during the crystallization. The pure **9** (by HPLC) was taken for second step of O-alkylation with 1-(2-Chloro-ethyl)-pyrrolidine (**10**)[10,11] to get pure drug Centchroman hydrochloride. The final drug was purified well to meet the latest pharmacopoeia requirement. All intermediates were well characterized. The whole strategy is given in **Scheme-II**



Scheme-II: Synthesis of Centchroman hydrochloride

In conclusion we have reported a practical synthesis of Centchroman of pharmacopoeia quality.

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