Supporting Information

For

Total Synthesis of Lasofoxifene and Nafoxidine

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Supporting Information:

3-(3-Methoxy-phenyl)-1-phenyl-propan-1-one (4)^[9]:

To a stirred solution of 3-Methoxy benzaldehyde (**3**) (20 g 0.14 mol) and Acetophenone (21.1 g 0.17 mol) in methanol (80 mL), 6M KOH solution (35 mL) was added slowly at 5-10 °C and then stirred for another 4 h at 5-10 °C. After completion of the reaction (monitored by TLC) solvent (methanol) was evaporated completely and the residue was extracted with ethyl acetate (2 x 200 mL), combined extracts were washed with 5% brine solution (100 mL) and DM water (100 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum gave the crude product. Crude product was purified on silica gel column (eluting solvent 10% ethyl acetate in hexane) to afford an yellow color desired product **4**. Yield: 30 g (88%); Description: Yellow solid; Mp: 56-58 °C; IR (in KBr, cm⁻¹): 2832, 1960, 1656, 1578, 1492, 1267, 770; ¹H NMR (400 MHz, CDCl₃) (δ ppm): 8.17 (d, *J*=7.74 Hz, 2H), 7.96 (d, *J*=7.80 Hz, 1H), 7.64-7.75 (m, 2H), 7.57 (t, *J*=7.45 Hz, 2H), 7.49 (s, 1H), 7.43 (d, *J*=7.58 Hz, 1H), 7.34 (t, *J*=7.66 Hz, 1H), 7.02 (d, *J*=7.87 Hz, 1H), 3.82 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) (δ ppm): 187.0, 161.9, 142.8, 136.7, 135.9, 134.3, 129.7, 129.4, 129.0, 123.3, 118.5, 113.3, 111.8, 56.0;

3-(3-Methoxy-phenyl)-1-phenyl-propan-1-one (5)^[9]:

To a solution of **4** (3-(3-Methoxy-phenyl)-1-phenyl-propan-1-one) (25 g) and ethanol (500 mL) 5% Pd/C (1.2 g) was added at RT, after 15 min H₂ gas was passed slowly at RT for 3 h. After completion of the reaction (monitored by TLC) Pd/C was filtered through celite bed and washed with ethanol (50 mL), total reaction mass was concentrated under vacuum to get the desired product **5**. Yield: 24 g (95%); Description: White solid; Mp: 65-67.5 °C; IR (in KBr, cm⁻¹): 2931, 1916, 1679, 1593, 1448, 1256, 746; ¹H NMR (400 MHz, CDCl₃) (δ ppm): 7.97 (d, *J*=7.55 Hz, 2H), 7.56 (t, *J*=7.34 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 2H), 7.26-7.21 (m, 1H), 6.88-6.75 (m, 3H), 3.80 (s, 3H, OCH₃), 3.30 (t, *J*=4.2 Hz, 2H), 3.06 (t, *J*=7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) (δ ppm): 197.6, 161.9, 141.2, 137.4, 132.9, 129.4, 128.6, 128.4, 120.2, 113.5, 111.3, 56.0, 41.2, 30.2;

4-[4-(2-Chloro-ethoxy)-phenyl]-7-methoxy-3-phenyl-1,2-dihydro-naphthalene (7)^[5]:

TiCl₃ (20.0 g, 0.12 mol) and Zn-Cu couple (20.0 g, 0.3 mol) were placed in a 500 mL round bottom flask under nitrogen. Dimethoxyethane (DME) (150 mL) was added slowly

(exothermic) and to this slurry crude **6** and **6a** (in 50 mL DME) was added at reflux for 30 min and resulting mixture was refluxed for 15 min. After completion of the reaction (monitored by TLC) the suspension was filtered and solvent evaporated to get the crude product, purification on silica gel Coolum (eluting solvent hexane only) afford desired product **7**. Yield: 2.8 g (35%); Description: White solid; Mp: 92.3-94.7 °C; IR (in KBr, cm⁻¹): 2832, 1610, 1504, 1239, 1108, 1041; ¹H NMR (400 MHz, CDCl₃) (δ ppm): 7.11(t, *J*=7.30 Hz, 2H), 7.05-6.96 (m, 5H), 6.77 (d, *J*=8.33 Hz, 3H), 6.70 (d, *J*=8.5 Hz, 1H), 6.59 (d, *J*=2.4 Hz, 1H), 4.20 (t, *J*=6.0 Hz, 2H), 3.80 (t, *J*=6.14 Hz, 2H), 3.82 (s, 3H), 2.95 (t, *J*=7.60 Hz, 2H), 2.78 (t, *J*=6.40 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) (δ ppm): 158.50, 156.78, 143.25, 137.76, 134.64, 134.52, 132.95, 132.33, 130.44, 128.32, 127.64, 127.47, 125.74, 114.25, 113.27, 110.83, 67.93, 55.31, 42.0, 30.80, 29.01;

Nafoxidine·HCl:

1-{2-[4-(6-Methoxy-2-phenyl-3,4-dihydro-naphthalen-1-yl)-phenoxy]-ethyl}-pyrrolidine·HCl (1**)**^[4]:

Under nitrogen atmosphere, a mixture of **7** (2 g) and pyrrolidine (15 mL) was stirred under reflux for 4 h. The reaction was monitored by TLC, after completion of the reaction the mixture was cooled to RT and concentrated under vacuum for recovery of pyrrolidine. To the residue added ethyl acetate (50 mL) and washed with saturated bi carbonate solution (70 mL) and DM water 50mL. The organic layer was separated and deride over sodium sulfate and concentrated under vacuum, to get the product free base.

Base product was diluted in 20 mL ethyl acetate, added 15% Ethyl acetate HCl for 10 min at 10-15° C and stirred for 15 min. filtered the solid, to get the desired product **1**. Yield: 1.8 g (88%); Description: Brown solid; Mp: 168.5-171.3 °C; IR (in KBr, cm⁻¹): 3393, 2943, 1608, 1490, 1238, 1037; ¹H NMR (400 MHz, CDCl₃) (δ ppm): 12.75 (s, 1H, HCl), 7.11 (d, *J*=7.36 Hz, 2H), 7.06 (d, *J*=7.0 Hz, 1H), 7.0 (m, 4H), 6.76 (m, 3H), 6.68 (d, *J*=8.56 Hz, 1H), 6.60 (d, *J*=2.12 Hz, 1H), 4.48 (m, 2H), 3.88 (m, 2H), 3.80 (s, 3H, OCH₃), 3.46 (m, 2H), 2.98-2.91 (m, 4H, Pyrrolidine), 2.78 (t, *J*=7.66 Hz, 2H), 2.25 (t, *J*=5.90 Hz, 2H), 1.69 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) (δ ppm):158.46, 155.83, 143.10, 137.67, 134.62, 134.41, 133.47, 132.41, 130.29, 128.25, 127.66, 127.39, 125.77, 114.04, 113.20, 110.84, 63.37, 55.29, 54.40, 53.92, 30.75, 28.92, 23.21;

1-{2-[4-(6-Methoxy-2-phenyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-phenoxy]-ethyl}-pyrrolidine (9) ^[4]:

An autoclave was charged with **1** (Nafoxidine) (1.0 g), 5% Pd/C (0.3 g) and ETOH+MEOH (100+50 mL) mixture. The vessel was sealed and then the whole mixture was stirred for 10 h at 50 °C under hydrogen atmosphere (10 Kg). After completion of the reaction (monitored by TLC) the reaction mixture was cooled to RT and filtered through a celite and washed with methanol (20 mL). The filtrate concentrated under reduced pressure to get the desired product **9**. Yield: 0.8 g (85%); Description: Color less thick liquid; IR (neat): 2932, 1608, 1506, 1460, 1240, 1178, 1155, 823; ¹H NMR (400 MHz, CDCl₃) (δ ppm): 7.16-7.14 (m, 3H, Ar), 6.86 (d, *J*=7.8 Hz, 1H, Ar), 6.80-6.75 (m, 3H, Ar), 6.68 (m, 1H, Ar), 6.54 (d, *J*=8.4 Hz, 2H, Ar), 6.30 (d, *J*=8.4 Hz, 2H, Ar), 4.23 (d, *J*=4.76 Hz, 2H), 3.98 (t, *J*=5.7 Hz, 2H, OCH₂), 3.81 (s, 3H, OCH₃), 3.35 (ddd, *J*=12.0, 4.9, 2.0 Hz, 1H), 3.07 (m, 2H), 2.83 (t, *J*=5.9 Hz, 2H), 2.63-2.59 (m, 4H, Pyrrolidine), 2.17 (m, 2H), 1.82-1.78 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) (δ ppm): 157.3, 156.5, 144.2, 137.6, 135.0, 133.2, 131.4, 131.2, 128.0, 127.9, 125.6, 113.0, 112.9, 112.0, 66.5, 55.2, 55.0, 54.4, 50.3, 45.4, 30.3, 23.4, 21.0;

Lasofloxifene: (2) (6-Phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol) ^[4]:

To a solution of methyl ether **9** (600 mg, 1.4 mmol), in DCM (5 mL) added BBr₃ in DCM (1.0 M, 8 mL) solution at -50 °C for 5 min. The reaction mixture was stirred for 3 h at 0 °C. After completion of the reaction (monitored by TLC), reaction mixture was poured into saturated sodium bicarbonate solution (25 mL) at 0°C. Then extracted with DCM (2X20 mL) and the organic layer was washed with brine solution (20mL). The organic layer dried over sodium sulfate and concentrated under vacuum to get the crude, crude crystallization in ethyl acetate to get the desired product **2** (Lasofloxifene). Yield: 430 mg (80%); Description: brown color solid; Mp: 132-134.3 °C; IR (in KBr, cm⁻¹): 3471, 2928, 1775, 1652, 1503, 1177, 757; ¹H NMR (400 MHz, CDCl₃) (δ ppm): 7.16-7.14 (m, 3H, Ar), 6.80-6.78 (m, 3H, Ar), 6.66 (s, 1H, Ar), 6.57 (dd, *J*=8.1, 2.4 Hz, 1H, Ar), 6.45 (d, *J*=8.32 Hz, 2H, Ar), 6.27 (d, *J*=8.32 Hz, 2H, Ar), 4.21 (d, *J*=4.56 Hz, 1H), 3.98 (m, 2H, OCH₂), 3.35 (ddd, *J*=11.4, 4.8, 2.0 Hz, 1H), 2.99-2.97 (m, 2H), 2.94-2.91 (m, 2H), 2.81 (m, 4H, Pyrrolidine), 2.13 (m, 1H), 1.82-1.76 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) (δ ppm): 156.6, 155.2, 144.8, 137.6, 134.6, 131.8, 131.4, 128.4, 128.2, 127.5, 126.0, 114.7, 113.9, 112.6, 65.8, 55.2, 54.2, 50.8, 45.8, 30.0, 23.5, 21.9.

Time 16.31
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 16384
SOLVENT CDCl₃
NS 48
DS 0
SWH 11990.407 Hz
FIDRES 0.731836 Hz
AQ 0.6832628 sec
RG 80.6
DW 41.700 usec
DE 6.00 usec
TE 297.3 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

CHANNEL f1
NUC1 1H
P1 9.00 usec
PL1 -2.00 dB
SFO1 400.1324708 MHz

F2 - Processing parameters
SI 16384
SF 400.1300089 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

F2 - Acquisition Parameters
Date 20151114
Time 16.40
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 32768
SOLVENT CDCl₃
NS 351
DS 0
SWH 27173.912 Hz
FIDRES 0.829282 Hz
AQ 0.6029812 sec
RG 1448.2
DW 18.400 usec
DE 6.00 usec
TE 297.3 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

CHANNEL f1
NUC1 13C
P1 9.70 usec
PL1 2.00 dB
SFO1 100.6228298 MHz

CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 17.70 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768

Date 20150912
Time 17.45
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 16384
SOLVENT CDCl₃
NS 48
DS 0
SWH 11990.407 Hz
FIDRES 0.731836 Hz
AQ 0.6832628 sec
RG 80.6
DW 41.700 usec
DE 6.00 usec
TE 294.7 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.00 usec
PL1 -2.00 dB
SFO1 400.1324708 MHz

F2 - Processing parameters
SI 16384
SF 400.1300089 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

F2 - Acquisition Parameters
Date 20150912
Time 17.53
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl₃
NS 263
DS 0
SWH 27173.912 Hz
FIDRES 0.414641 Hz
AQ 1.2059124 sec
RG 3251
DW 18.400 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 13C
P1 9.70 usec
PL1 2.00 dB
SFO1 100.6228298 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 17.70 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768

Time 15.03
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 48
DS 0
SWH 11990.407 Hz
FIDRES 0.731836 Hz
AQ 0.6832628 sec
RG 256
DW 41.700 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.00 usec
PL1 -2.00 dB
SFO1 400.1324708 MHz

F2 - Processing parameters
SI 16384
SF 400.1300089 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

F2 - Acquisition Parameters
Date 20150904
Time 17.11
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 124
DS 0
SWH 27173.912 Hz
FIDRES 0.414641 Hz
AQ 1.2059124 sec
RG 2048
DW 18.400 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 13C
P1 9.70 usec
PL1 2.00 dB
SFO1 100.6228298 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 17.70 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 400.1316005 MHz

Time 16.37
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 16384
SOLVENT CDCl₃
NS 38
DS 0
SWH 11990.407 Hz
FIDRES 0.731836 Hz
AQ 0.6832628 sec
RG 256
DW 41.700 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.00 usec
PL1 -2.00 dB
SFO1 400.1324708 MHz

F2 - Processing parameters
SI 16384
SF 400.1300089 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

F2 - Acquisition Parameters
Date 20150909
Time 9.25
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl₃
NS 157
DS 0
SWH 27173.912 Hz
FIDRES 0.414641 Hz
AQ 1.2059124 sec
RG 2298.8
DW 18.400 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 13C
P1 9.70 usec
PL1 2.00 dB
SFO1 100.6228298 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 16.98 dB
PL13 17.70 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768

—— SampleName SVN-NX- ST-V#Blank; Vial 21; Date Acquired 9/8/2015 07:38:47 PM IST
 —— SampleName SVN-NX- ST-V#1; Vial 20; Date Acquired 9/8/2015 07:12:08 PM IST

Peak Results

	Name	RT	Height	Area	% Area	RT Ratio
1	Peak1	2.94	225	1491	0.01	0.84
2	ST-V	3.51	803032	14257231	99.99	
3						
Sum				14258722	100	

Analysed by:

Peak Results

	Name	RT	Height	Area	% Area	RT Ratio
1	Peak1	11.29	108991	647927	1.88	0.97
2	ST-IV	11.58	4695522	33196506	96.40	
3	Peak3	11.84	79144	469623	1.36	1.02
4	Peak4	12.07	8112	42686	0.12	1.04
5	Peak5	12.37	8394	40048	0.12	1.07
6	Peak6	12.57	2416	10063	0.03	1.09
7	Peak7	14.35	4627	29036	0.08	1.24
Sum				34435889	100	

Analysed by: