Supporting Information

Synthesis of Entacapone by Pd-catalyzed Heck coupling reaction.

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1.General Information.

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. TLC or HPLC routinely checked the purity of all compounds. IR spectra were recorded on a Perkin-Elmer model 2000 instrument in KBr phase. ^1H -NMR (400 MHz) and ^{13}C -NMR (100MHz) spectra were recorded in CDCl_3 or DMSO using Bruker instrument and Mass spectra were recorded on a Perkin-Elmer mass spectrometer operating at 70 eV.

2.Typical procedures and Spectral Characterizations for Intermediates and Entacapone.

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. TLC or HPLC routinely checked the purity of all compounds. IR spectra were recorded on a Perkin-Elmer model 2000 instrument in KBr phase. ^1H -NMR (400 MHz) and ^{13}C -NMR (100MHz) spectra were recorded in CDCl_3 or DMSO using Bruker instrument and Mass spectra were recorded on a Perkin-Elmer mass spectrometer operating at 70 eV.

Preparation of 2-Cyano-*N,N*-diethylacrylamide (3):

Trifluoroacetic acid was added to *N*-methylaniline at 0-5°C under nitrogen atmosphere. Stirred for 2hrs at 0-5°C. Distill off the solvent to get the crude salt. To this crude, hexane(100 ml) was added and stirred for 30 minutes. Filtered the precipitated salt

under nitrogen atmosphere and directly taken into THF (600.0ml) solution having *N,N*-diethyl-2-cyanoacetamide(19.1_g, 0.136mol) and para formaldehyde (18.36_g, 0.612 mol). Stitted for 2-3hrs at 60-65°C. Reaction mass cooled and water (200 ml) and ~~Ethyl~~ethyl acetate (400ml) were added. Separated the Organic layer and washed with brine solution (100 ml). Dried the organic layer distill off the solvent to get the crude , which is purified by High vacuum distillation. (Wt 12.0_gms). (It should be kept in cooling under nitrogen atmosphere and is stable for 1 month).

IR (KBr) (cm⁻¹): 3113, 2226, 1943, 1781, 1642; ¹H-NMR (400 MHz, CDCl₃): δ 1.19 (s, 3H), 1.27 (s, 3H), 3.34 (s, 4H), 6.35 (s, 1H), 6.47 (s, 1H); MS (ESI) *m/z*: 153.1 (M+1).

Preparation of (*E*)-2-cyano-*N,N*-diethyl-3-(4-hydroxy-3-methoxy-5-nitrophenyl)acrylamide (6):

To a solution of acetic acid (5.0ml) and (*E*)- 2-cyano-*N,N*-diethyl-3-(4-hydroxy-3-methoxyphenyl)acrylamide **4** (2.0_g, 0.0072 mol), 60% HNO₃ (1.13_g, 0.0108 mol) was added at 15°C for 10 minutes. Stirred for 5-10 minutes at 15°C. Reaction mass quenched into ice water (25.0ml) and stirred for 30 minutes. The precipitate obtained was filter and dried to get crude (mp.104.4-108.4°C) ^[3]. Which is purified in ethyl acetate to get the pure (*E*)-2-cyano-*N,N*-diethyl-3-(4-hydroxy-3-methoxy-5-nitrophenyl)acrylamide **6** (Wt. 1.68 g, mp. 129.6-131.3°C)^[2] HPLC Purity: 99.86%).

IR (KBr) cm⁻¹: 3120, 2203, 1637, 1547, 1261; ¹H-NMR (400 MHz, DMSO): δ 1.14 (s, 6H), 3.41 (s, 4H), 3.91 (s, 3H), 7.70 (s, 1H), 7.85 (s, 1H), 8.09 (s, 1H), 11.4 (s, 1H); ¹³C NMR (100 MHz, DMSO): δ 56.98, 105.58, 115.76, 116.69, 119.08, 122.95, 137.41, 145.64, 147.61, 149.83, 162.79; MS (ESI) *m/z*: 320.3 (M+1).

Preparation of Entacapone (1):

———To a solution of Dichloromethane (6.0 ml) and pyridine (2.5 ml), (*E*)-2-cyano-*N,N*-diethyl-3-(4-hydroxy-3-methoxy-5-nitrophenyl)acrylamide **10** (1.0g, 0.0031 mol) was added at 0-5°C. Aluminiumchloride (1.58g, 0.0118 mol) was added at 0-5°C over a period of 15-20 minutes and maintained for 30 minutes. Reaction mass temperature raised to RT and maintained for 2-3hrs at 40-45°C. After completion of reaction, reaction mass quenched into dilute hydrochloric acid and ice water (3.0 ml). Separated the organic layer and distill off the solvent to get the pure Entacapone **1**(0.9g).

¹H-NMR (400 MHz, CDCl₃): δ 1.30 (s, 1H), 3.50 (s, 4H), 6.22 (s, 1H), 7.57 (s, 1H), 7.88 (s, 1H), 8.12 (s, 1H), 10.93 (s, 1H).

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3. Copies of NMR spectra for Intermediates and Entacapone

SINO LIFE SCIENCES LIMITED
 DISCOVERY ANALYTICAL
 Sample Name: SVN-1006 (NP) /ST-II (A) /01
 Test Type: 1H-NMR
 Run Date: 15-Jul-2013
 Analyst: HAH

hah
 15-jul-2013

Current Data Parameters
 NAME: h8000713
 EXPNO: 1
 PROCNO: 1
 F2 - Acquisition Parameters
 Date_: 20130715
 Time: 16.43
 INSTRUM: av400
 PROBHD: 5 mm BBO BB-1H
 PULPROG: zg30
 TD: 16384
 SOLVENT: CDCl3
 NS: 22
 DS: 0
 SWH: 11990.407 Hz
 FIDRES: 0.731636 Hz
 AQ: 0.6632628 sec
 RG: 256
 DW: 41.700 usec
 DE: 6.00 usec
 TE: 295.5 K
 D1: 1.00000000 sec
 MCREST: 0.00000000 sec
 MCWRK: 0.01500000 sec
 ----- CHANNEL f1 -----
 NUC1: 1H
 P1: 8.50 usec
 PL1: -2.00 dB
 SF01: 400.1324708 MHz
 F2 - Processing parameters
 SI: 16384
 SF: 400.1300155 MHz
 WDW: EM
 SSB: 0
 LB: 1.00 Hz
 GB: 0
 PC: 1.00
 1D NMR plot parameters
 CX: 20.00 cm
 CY: 6.00 cm
 F1P: 12.951 ppm
 F1: 5181.95 Hz
 F2P: -1.144 ppm
 F2: -457.61 Hz
 FPMCH: 0.70472 ppm/cm
 HZCM: 281.97778 Hz/cm

SHRI LIFE SCIENCES LIMITED
DISCOVERY ANALYTICAL
Sample Name: SVN-1006/NP/ST-II B/02
Test Type: 1H-NMR
Run Date: 06-Aug-2013
Analyst: NARENDRA

06-Aug-2013

Current Data Parameters
NAME: 1n2560813
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20130806
Time: 9.41
INSTRUM: av400
PROBHD: 5 mm BBO BB-1H
PULPROG: zg30
TD: 16384
SOLVENT: DMSO
NS: 44
DS: 0
SWH: 11990.407 Hz
FIDRES: 0.731836 Hz
AQ: 0.6832628 sec
RG: 256
DN: 41.700 usec
DE: 6.00 usec
TE: 294.2 K
D1: 1.00000000 sec
MCREST: 0.00000000 sec
MCMR: 0.01500000 sec

===== CHANNEL f1 =====
NUC1: 1H
P1: 8.50 usec
PL1: -2.00 dB
SFO1: 400.1324708 MHz

F2 - Processing parameters
SI: 16384
SF: 400.1300057 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.00

1D NMR plot parameters
CX: 20.00 cm
CY: 6.00 cm
F1P: 11.522 ppm
F1: 4610.40 Hz
F2P: -0.882 ppm
F2: -352.74 Hz
PPMCM: 0.62019 ppm/c
HZCM: 248.15736 Hz/cm

SUVEN LIFE SCIENCES LIMITED
DISCOVERY ANALYTICAL
Sample Name: SVN-1006/NP/ST-II B/02
Test Type: 13C-NMR
Run Date: 06-Aug-2013
Analyst: NARENDRA

Current Data Parameters
NAME: In2580813
EXPNO: 3
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20130807
Time: 9.06
INSTRUM: mv400
PROBHD: 5 mm BBO BB-1H
PULPROG: zgpg30
TD: 262144
SOLVENT: DMSO
NS: 8827
DS: 0
SWH: 28248.568 Hz
FIDRES: 0.107760 Hz
AQ: 4.639989 sec
RG: 4096
DM: 17.700 usec
DE: 6.00 usec
TE: 296.0 K
d1: 1.0000000 sec
d11: 0.0300000 sec
WDEXT: 0.0000000 sec
WDEWK: 0.0150000 sec

===== CHANNEL f1 =====
NUC1: 13C
P1: 9.70 usec
PL1: 2.00 dB
SF01: 100.6218241 MHz

===== CHANNEL f2 =====
CPOPRG2: waltz16
NUC2: 1H
PCPD2: 80.00 usec
PL2: -2.00 dB
PL12: 18.00 dB
PL13: 17.70 dB
SF02: 400.1316005 MHz

F2 - Processing parameters
SI: 131072
SF: 100.6127826 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.40

1D NMR plot parameters
CX: 20.00 cm
CY: 25.00 cm
F1P: 204.860 ppm
F1: 20611.90 Hz
F2P: -6.203 ppm
F2: -825.37 Hz
RGMCN: 10.65315 ppm/cm
HZCN: 1071.84351 Hz/cm

SVN LIFE SCIENCES LIMITED
 DISCOVERY ANALYTICAL
 Sample Name: SVN-1006 (NP) /ST-III B # AA
 Test Type: 1H-NMR
 Run Date: 17-Aug-2013
 Analyst: HARI

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 17-Aug-2013

Current Data Parameters
 NAME: 1H8210813
 EXPNO: 1
 PROCNO: 1

F2 - Acquisition Parameters
 Date_: 20130817
 Time: 15.51
 INSTRUM: av400
 PROBHD: 5 mm BBO BB-1H
 PULPROG: zg30
 TD: 16384
 SOLVENT: DMSO
 NS: 44
 DS: 0
 SWH: 11990.407 Hz
 FIDRES: 0.731836 Hz
 AQ: 0.6832628 sec
 RG: 322.5
 OW: 41.700 usec
 DE: 6.00 usec
 TE: 297.8 K
 D1: 1.00000000 sec
 MCREST: 0.00000000 sec
 MCWAK: 0.01500000 sec

----- CHANNEL f1 -----
 NUC1: 1H
 P1: 8.50 usec
 PL1: -2.00 dB
 SFO1: 400.1324708 MHz

F2 - Processing parameters
 SI: 16384
 SF: 400.1300064 MHz
 WDW: EM
 SSB: 0
 LB: 1.00 Hz
 GB: 0
 PC: 1.00

1D NMR plot parameters
 CX: 20.00 cm
 CY: 25.00 cm
 F1P: 12.951 ppm
 F1: 5181.95 Hz
 F2P: -1.144 ppm
 F2: -457.61 Hz
 APMCH: 0.70472 ppm/cm
 HZCM: 281.97778 Hz/cm

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DISCOVERY ANALYTICAL
Sample Name: SVN-1006/NP/ST-1118/RC/AA
Test Type: 13C-NMR
Run Date: 22-Aug-2013
Analyst: NARENDRA

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22-Aug-2013

Current Data Parameters
NAME: 1M5100813
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20130822
Time: 10.13
INSTRUM: av400
PROBHD: 5 mm BBO BB-1H
PULPROG: zgpg30
TD: 262144
SOLVENT: DMSO
NS: 120
DS: 0
SWH: 26248.588 Hz
FIDRES: 0.107760 Hz
AQ: 4.6399989 sec
RG: 9195.2
DM: 17.700 usec
DE: 6.00 usec
TE: 280.4 K
D1: 1.00000000 sec
d11: 0.03000000 sec
NCHST: 0.00000000 sec
NCHPK: 0.01500000 sec

===== CHANNEL f1 =====
NUC1: 13C
P1: 9.70 usec
PL1: 2.00 dB
SFO1: 100.6218241 MHz

===== CHANNEL f2 =====
CPDPRG2: waltz16
NUC2: 1H
PCPD2: 89.00 usec
PL2: -2.00 dB
PL12: 18.00 dB
PL13: 17.70 dB
SFO2: 400.1315005 MHz

F2 - Processing parameters
SI: 131012
SF: 100.6127826 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.40

1D NMR plot parameters
CX: 20.00 cm
CY: 10.00 cm
FID: 226.763 cm
F1: 22815.21 Hz
F2: -8.962 cm
F3: -980.66 Hz
XNOM: 51.785/1 cm/cm
YOM: 1189.79321 Hz/cm

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DISCOVERY ANALYTICAL

Sample Name: ENTACAPONE/01

Test Type: 1H-NMR

Run Date: 27-Aug-2013

Analyst: NARENDRA

27-Aug-2013

Current Data Parameters

NAME: 1h13730813
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters

Date_: 20130827
Time: 11:10
INSTRUM: av400
PROBHD: 5 mm BBO BB-1H
PULPROG: zg30
TD: 16384
SOLVENT: CDCl3
NS: 105
DS: 0
SMH: 11990.407 Hz
FIDRES: 0.731836 Hz
AQ: 0.6830626 sec
RG: 228.1
DM: 41.700 usec
DE: 6.00 usec
TE: 294.2 K
D1: 1.00000000 sec
MCREST: 0.00000000 sec
MCWIR: 0.01500000 sec

***** CHANNEL f1 *****

NUC1: 1H
P1: 8.50 usec
PL1: -2.00 dB
SFO1: 400.1324708 MHz

F2 - Processing parameters

SI: 16384
SF: 400.1300148 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.00

1D NMR plot parameters

CX: 20.00 cm
CY: 6.00 cm
F1P: 12.905 ppm
F1: 5163.94 Hz
F2P: -0.925 ppm
F2: -370.10 Hz
PRMCM: 0.69153 ppm/cm
HZCM: 276.70172 Hz/cm