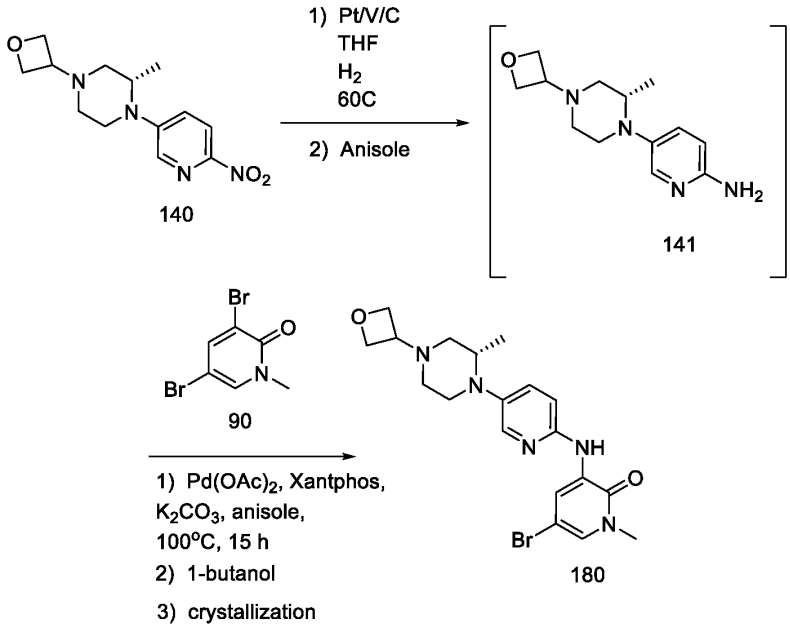

1) Pt/V/C
THF
H_2
60C
2) Anisole
140
141
90
1) $Pd(OAc)_2$, Xantphos,
K_2CO_3, anisole,
100°C, 15 h
2) 1-butanol
3) crystallization
180

FIG. 1

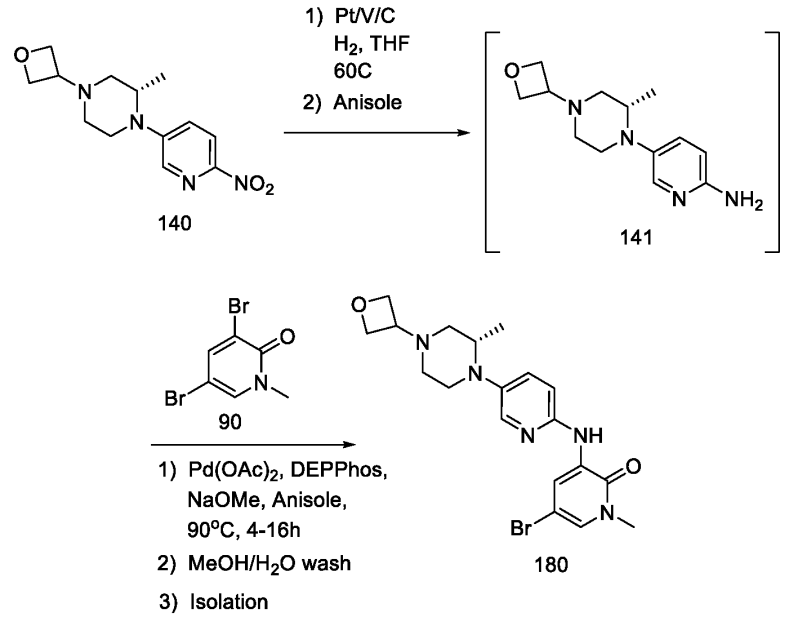

1) Pt/V/C
H_2, THF
60C
2) Anisole
140
141
90
1) $Pd(OAc)_2$, DEPPhos,
NaOMe, Anisole,
90°C, 4-16h
2) MeOH/H_2O wash
3) Isolation
180

FIG. 2

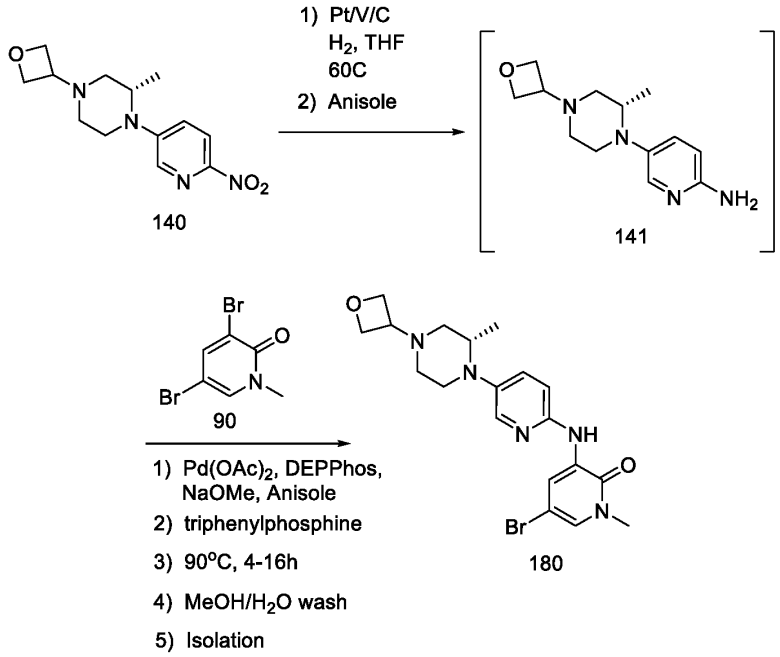

1) Pt/V/C
H2, THF
60C
2) Anisole
140
141
90
1) Pd(OAc)2, DEPPhos,
NaOMe, Anisole
2) triphenylphosphine
3) 90°C, 4-16h
4) MeOH/H2O wash
5) Isolation
180

FIG. 3

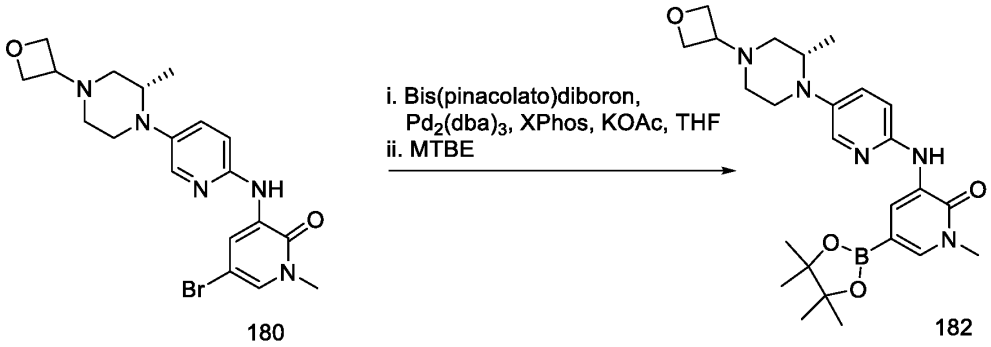

i. Bis(pinacolato)diboron,
Pd2(dba)3, XPhos, KOAc, THF
ii. MTBE
180
182

FIG. 4

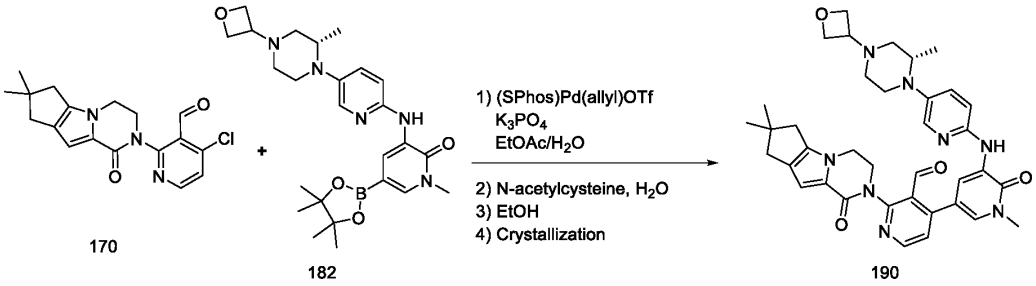


FIG. 5A

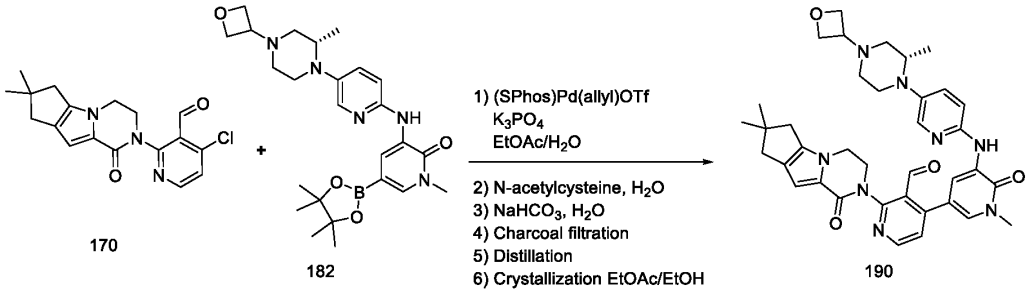


FIG. 5B

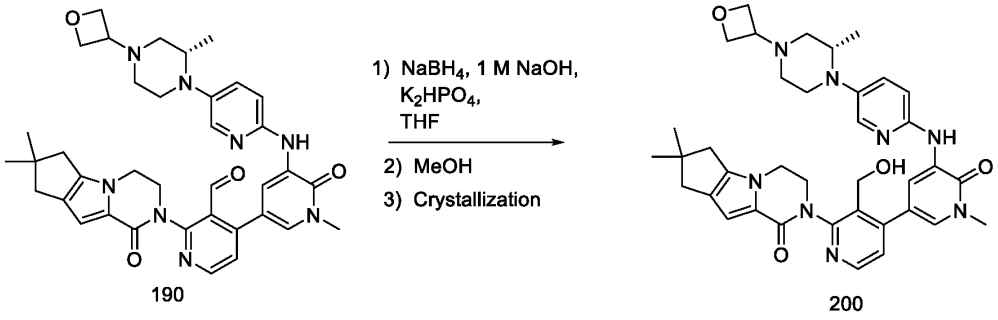


FIG. 6

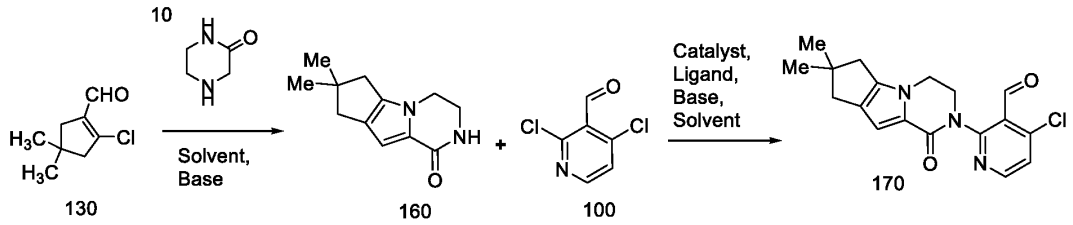

10
CHO
Cl
H_3C
H_3C
130
Solvent,
Base
Me
Me
NH
O
160
Cl
Cl
O
N
100
Catalyst,
Ligand,
Base,
Solvent
Me
Me
N
O
N
O
Cl
170

FIG. 7

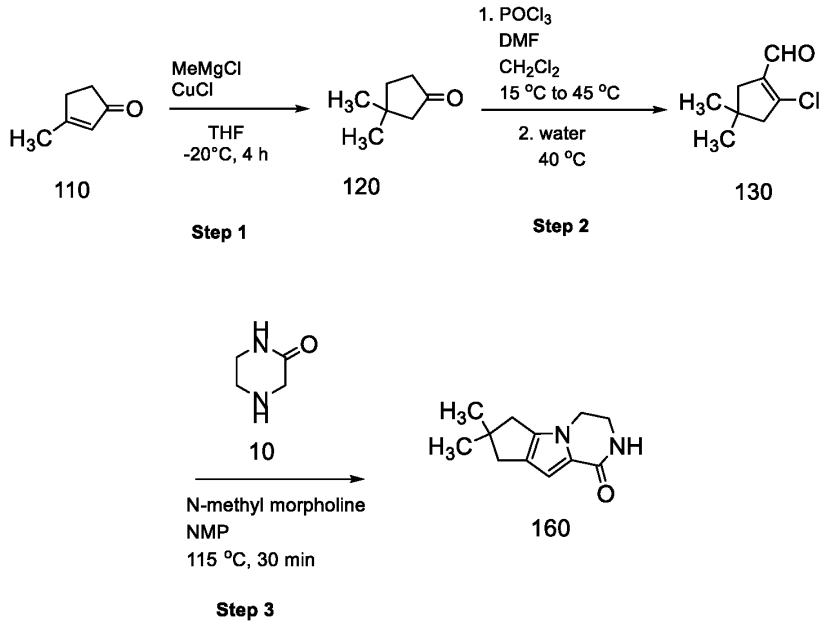

H_3C
O
110
MeMgCl
CuCl
THF
-20°C, 4 h
Step 1
H_3C
H_3C
O
120
1. $POCl_3$
DMF
CH_2Cl_2
15 °C to 45 °C
2. water
40 °C
Step 2
CHO
Cl
H_3C
H_3C
130
10
N-methyl morpholine
NMP
115 °C, 30 min
Step 3
H_3C
H_3C
N
NH
O
160

FIG. 8

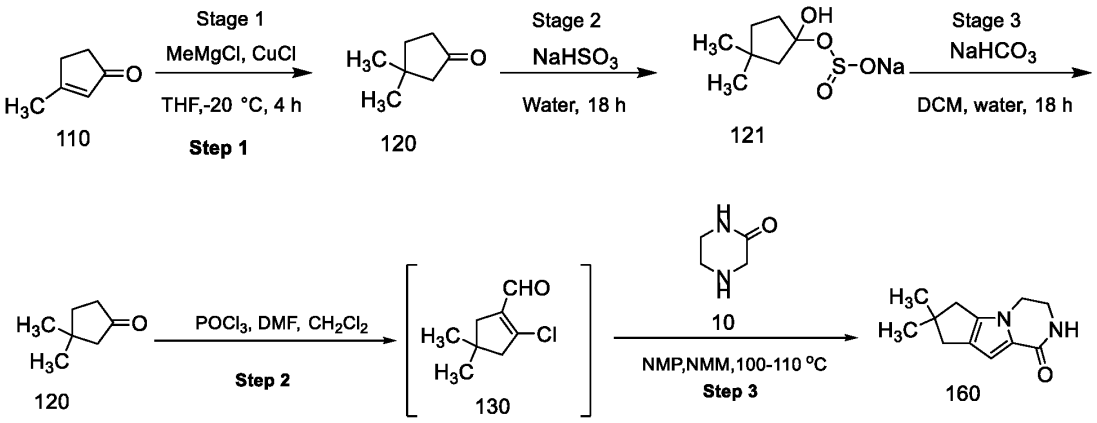

Stage 1
MeMgCl, CuCl
THF,-20 °C, 4 h
Step 1
Stage 2
NaHSO3
Water, 18 h
Stage 3
NaHCO3
DCM, water, 18 h
110
120
121
POCl3, DMF, CH2Cl2
Step 2
130
10
NMP,NMM,100-110 °C
Step 3
160

FIG. 9

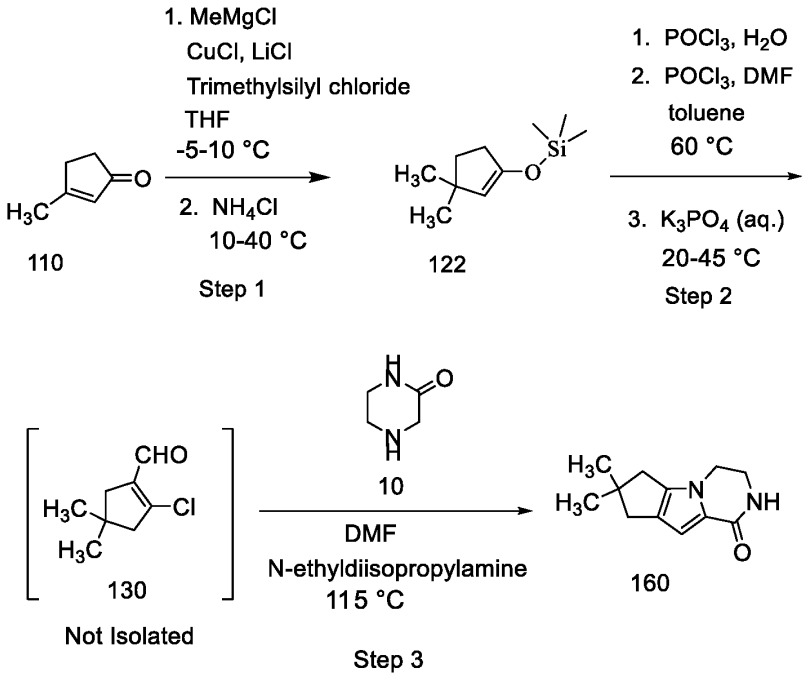

1. MeMgCl
CuCl, LiCl
Trimethylsilyl chloride
THF
-5-10 °C
2. NH4Cl
10-40 °C
Step 1
110
122
1. POCl3, H2O
2. POCl3, DMF
toluene
60 °C
3. K3PO4 (aq.)
20-45 °C
Step 2
130
Not Isolated
10
DMF
N-ethyldiisopropylamine
115 °C
Step 3
160

FIG. 10

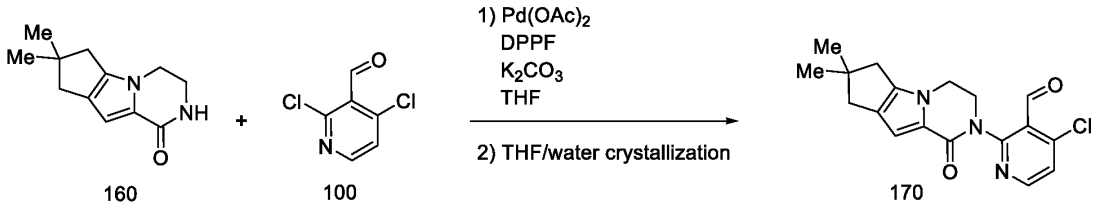


FIG. 11

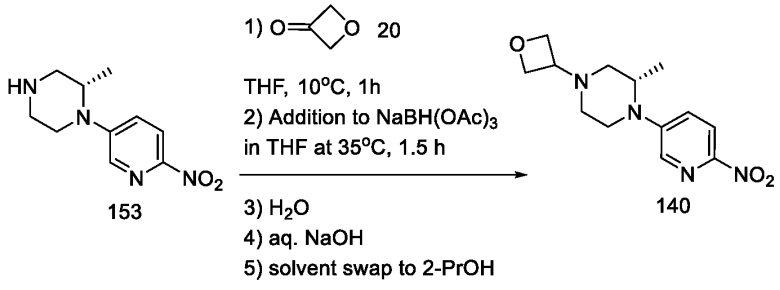


FIG. 12A

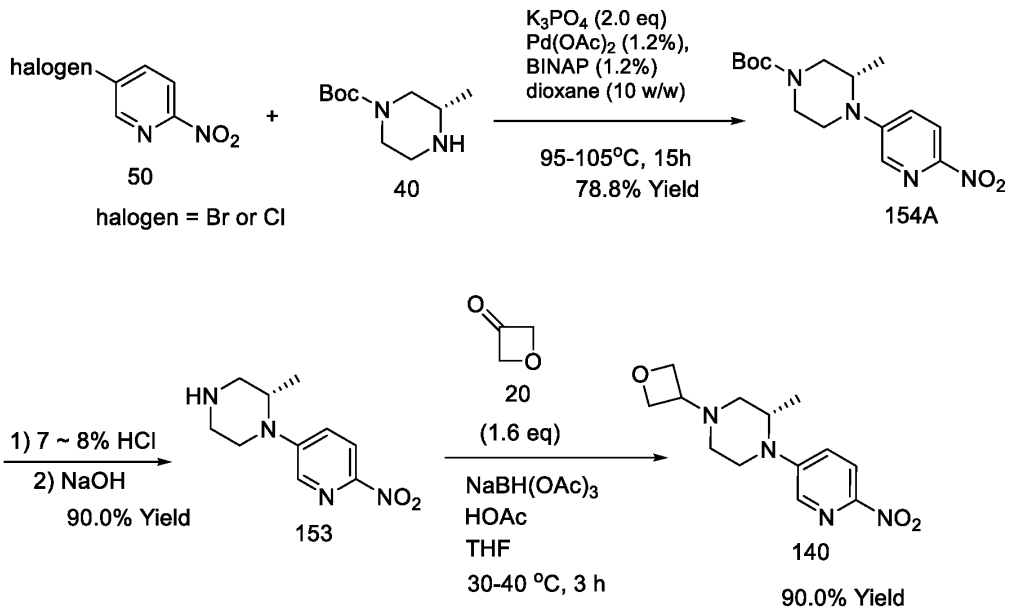


FIG. 12B

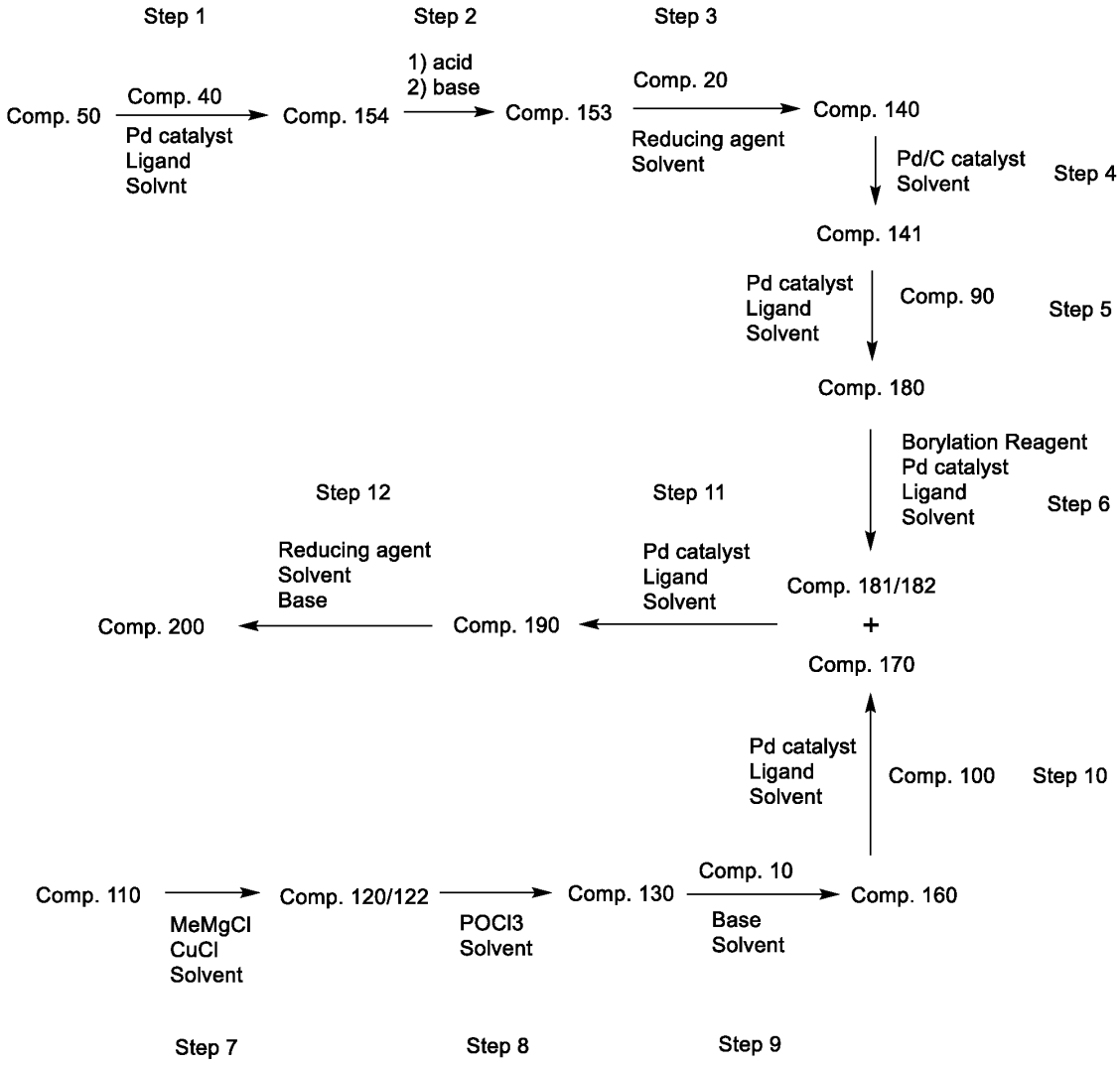

Step 1
Step 2
Step 3
Comp. 50
Comp. 40
Pd catalyst
Ligand
Solvnt
Comp. 154
1) acid
2) base
Comp. 153
Comp. 20
Reducing agent
Solvent
Comp. 140
Pd/C catalyst
Solvent
Step 4
Comp. 141
Pd catalyst
Ligand
Solvent
Comp. 90
Step 5
Comp. 180
Borylation Reagent
Pd catalyst
Ligand
Solvent
Step 6
Step 12
Step 11
Reducing agent
Solvent
Base
Pd catalyst
Ligand
Solvent
Comp. 200
Comp. 190
Comp. 181/182
+
Comp. 170
Pd catalyst
Ligand
Solvent
Comp. 100
Step 10
Comp. 110
MeMgCl
CuCl
Solvent
Comp. 120/122
POCl3
Solvent
Comp. 130
Comp. 10
Base
Solvent
Comp. 160
Step 7
Step 8
Step 9

FIG. 13

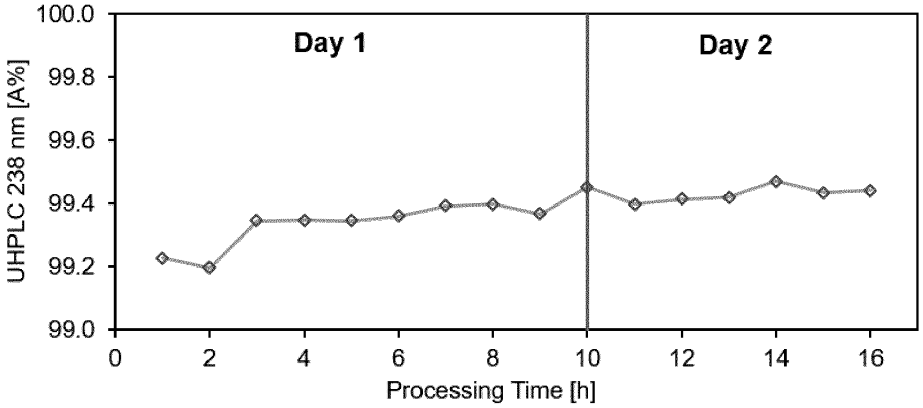
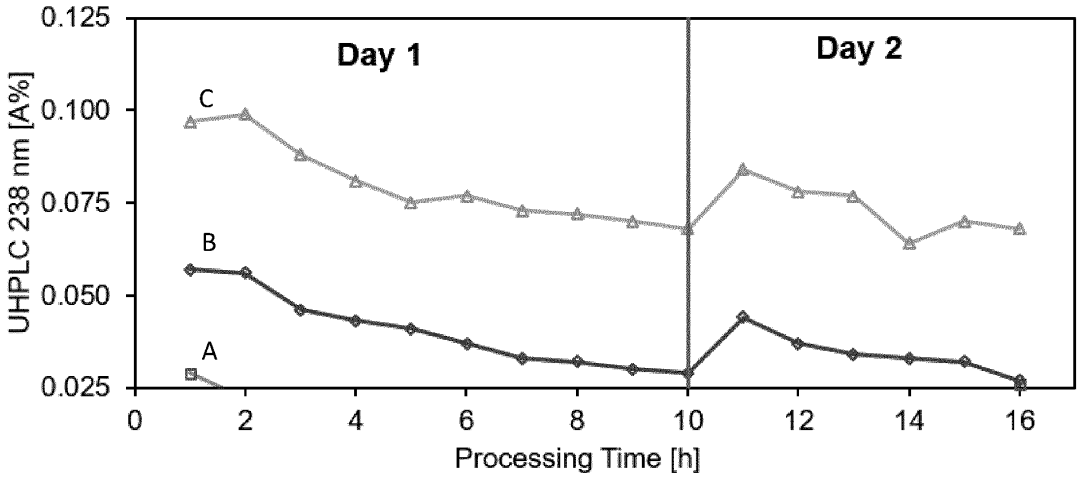


FIG. 14A



A: Compound 140 B: Dimer impurity C: Combined azo+azoxy impurities

FIG. 14B

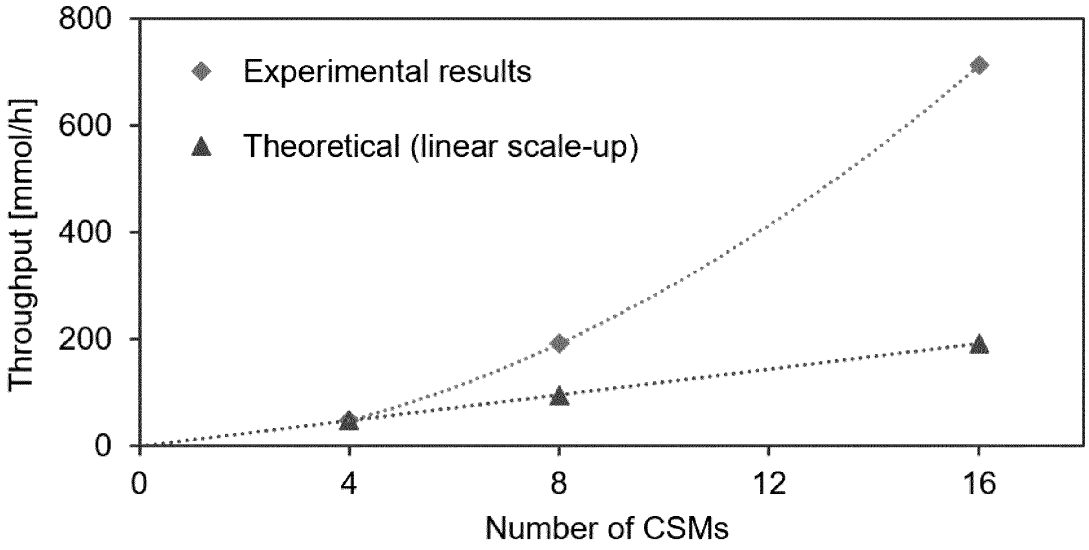

800
600
400
200
0
Throughput [mmol/h]
Experimental results
Theoretical (linear scale-up)
0
4
8
12
16
Number of CSMs

FIG. 15

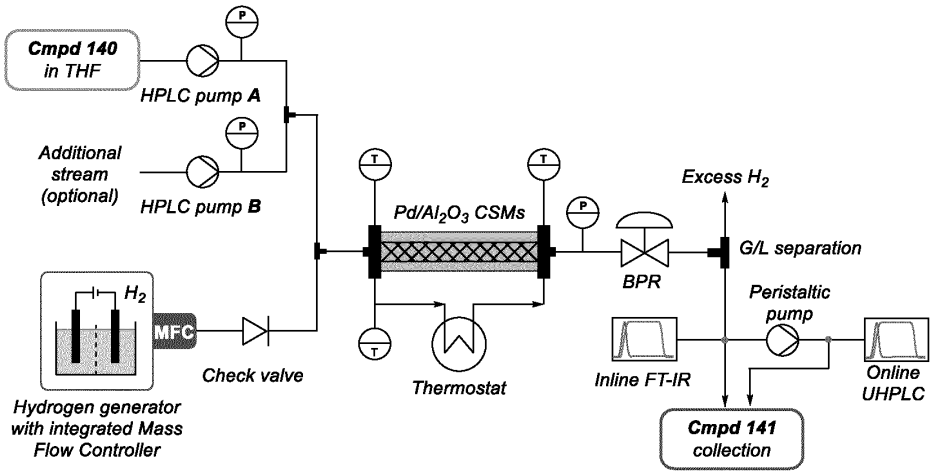

Cmpd 140 in THF
HPLC pump A
Additional stream (optional)
HPLC pump B
H2
MFC
Check valve
Hydrogen generator with integrated Mass Flow Controller
Pd/Al2O3 CSMs
Thermostat
Excess H2
BPR
G/L separation
Peristaltic pump
Inline FT-IR
Online UHPLC
Cmpd 141 collection

FIG. 16

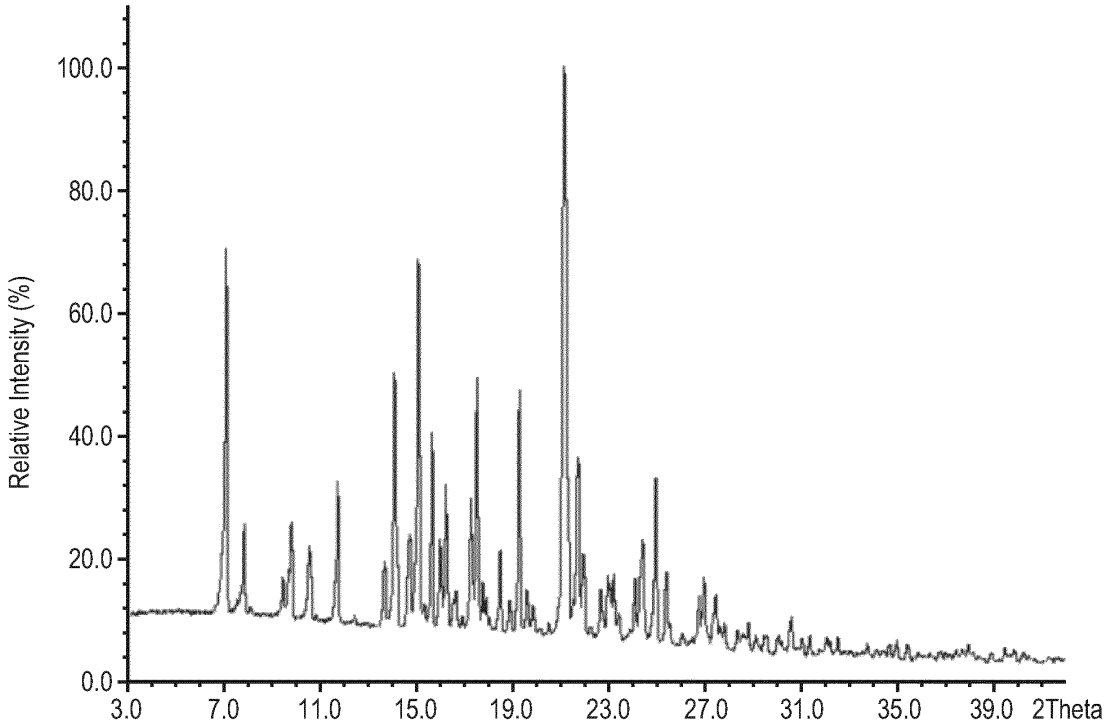

Relative Intensity (%)
100.0
80.0
60.0
40.0
20.0
0.0
3.0
7.0
11.0
15.0
19.0
23.0
27.0
31.0
35.0
39.0
2Theta

FIG. 17

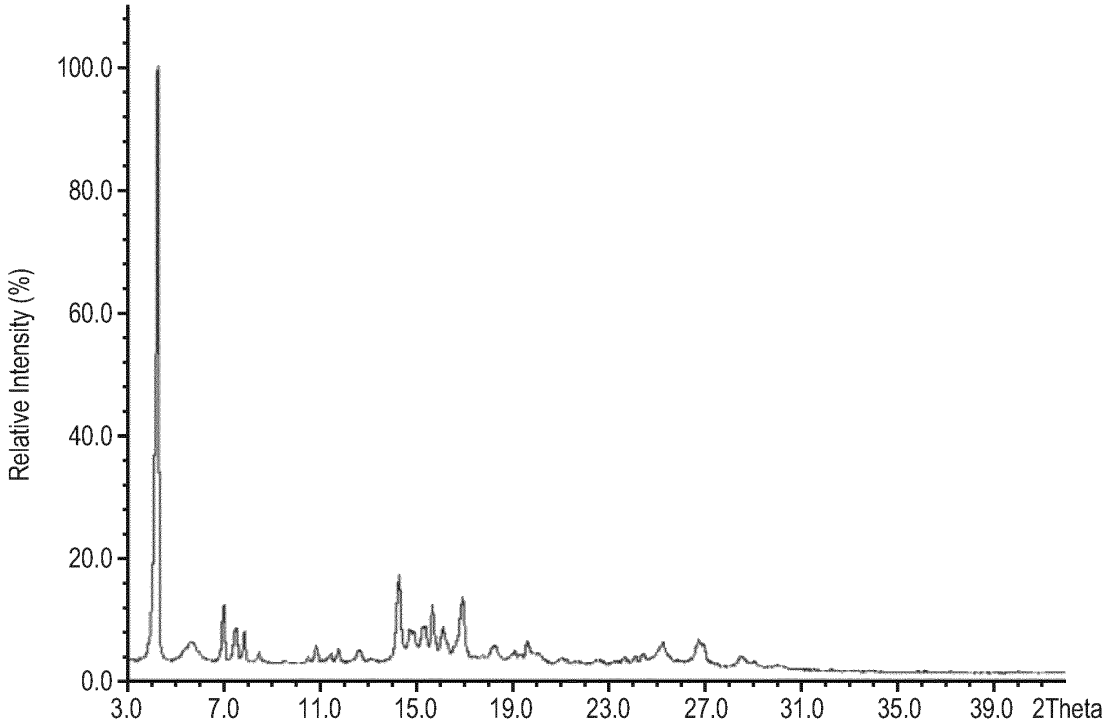

Relative Intensity (%)
100.0
80.0
60.0
40.0
20.0
0.0
3.0
7.0
11.0
15.0
19.0
23.0
27.0
31.0
35.0
39.0
2Theta

FIG. 18

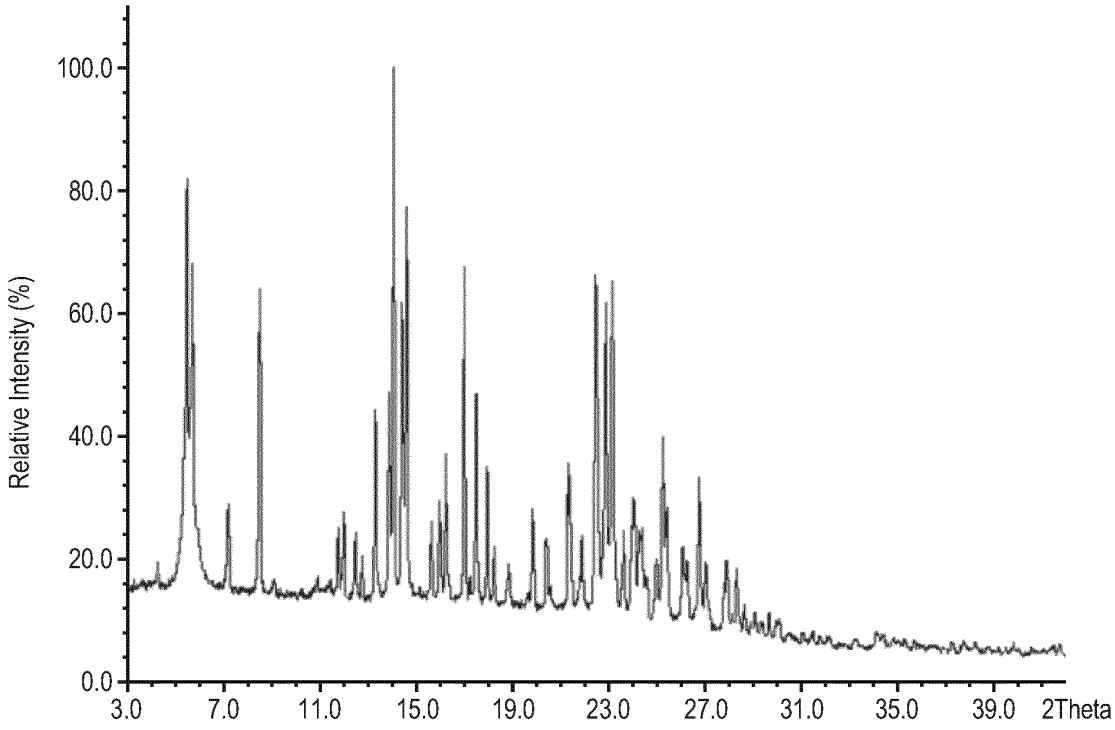

Relative Intensity (%)
100.0
80.0
60.0
40.0
20.0
0.0
3.0
7.0
11.0
15.0
19.0
23.0
27.0
31.0
35.0
39.0
2Theta

FIG. 19

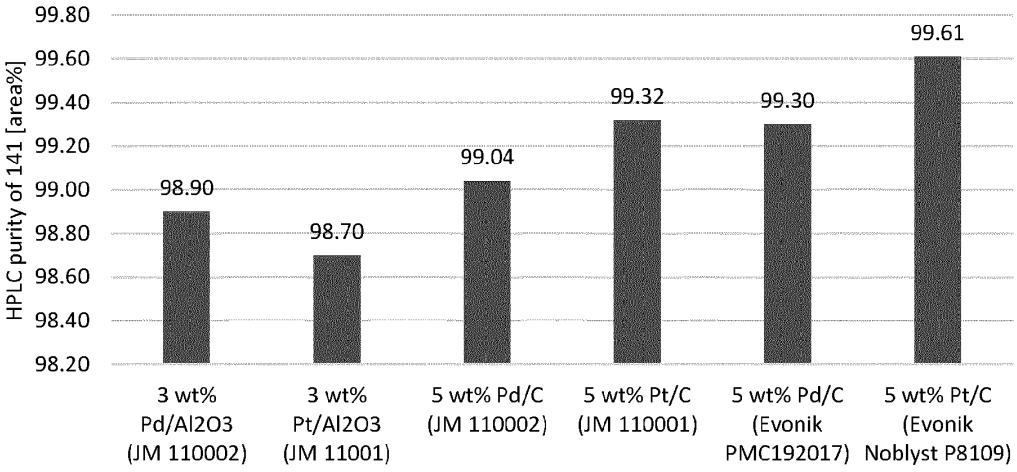

99.80
99.60
99.40
99.20
99.00
98.80
98.60
98.40
98.20
HPLC purity of 141 [area%]
98.90
98.70
99.04
99.32
99.30
99.61
3 wt% Pd/Al2O3 (JM 110002)
3 wt% Pt/Al2O3 (JM 11001)
5 wt% Pd/C (JM 110002)
5 wt% Pt/C (JM 110001)
5 wt% Pd/C (Evonik PMC192017)
5 wt% Pt/C (Evonik Noblyst P8109)

FIG. 20

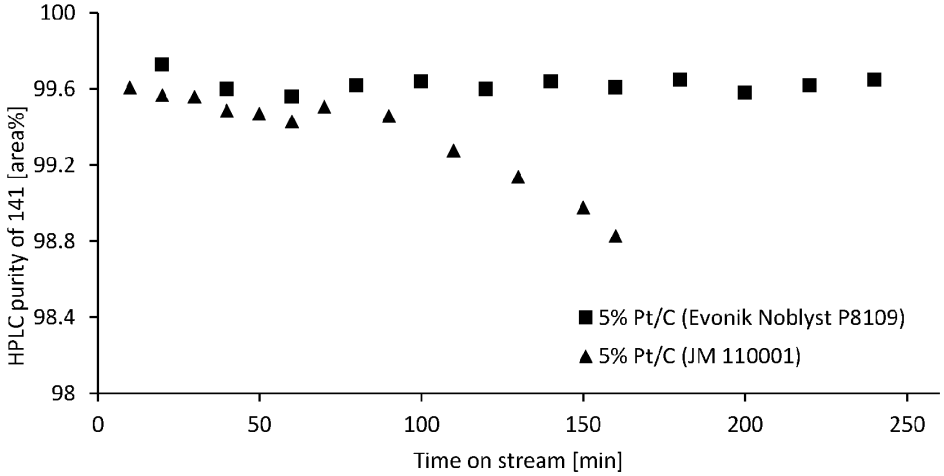

100
99.6
99.2
98.8
98.4
98
HPLC purity of 141 [area%]
0
50
100
150
200
250
Time on stream [min]
5% Pt/C (Evonik Noblyst P8109)
5% Pt/C (JM 110001)

FIG. 21

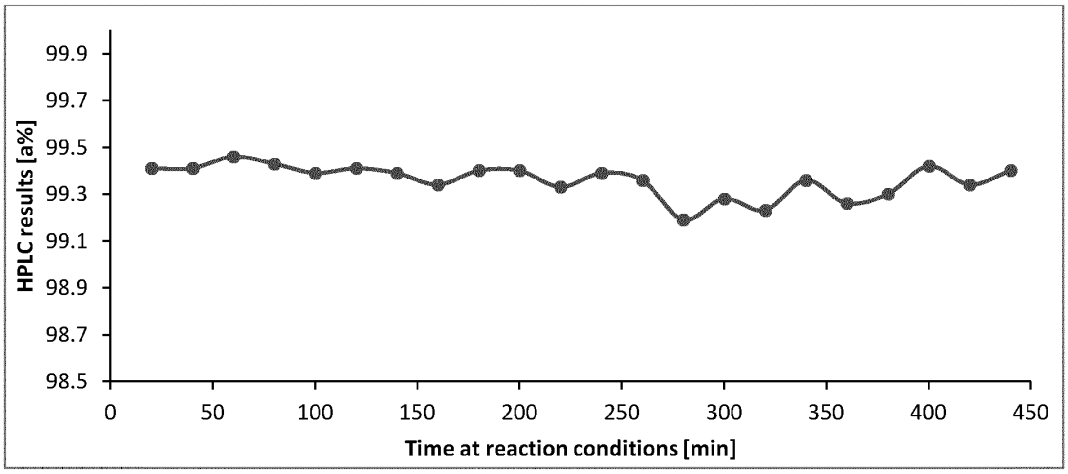

HPLC results [a%]
99.9
99.7
99.5
99.3
99.1
98.9
98.7
98.5
0
50
100
150
200
250
300
350
400
450
Time at reaction conditions [min]

FIG. 22

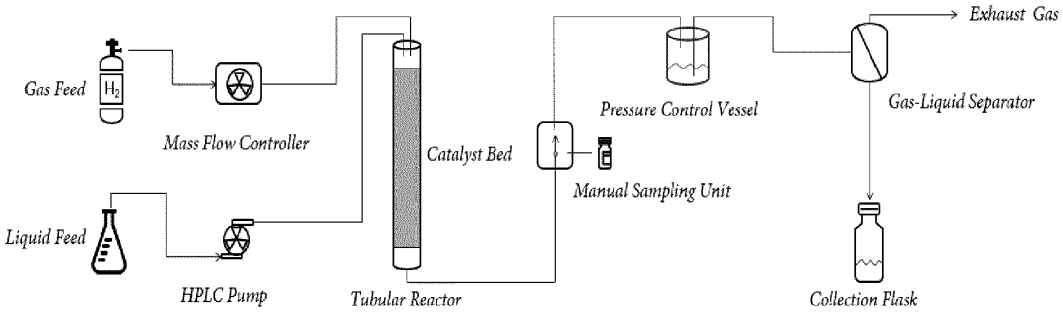

Gas Feed
H_2
Mass Flow Controller
Liquid Feed
HPLC Pump
Tubular Reactor
Catalyst Bed
Pressure Control Vessel
Manual Sampling Unit
Gas-Liquid Separator
Exhaust Gas
Collection Flask

FIG. 23