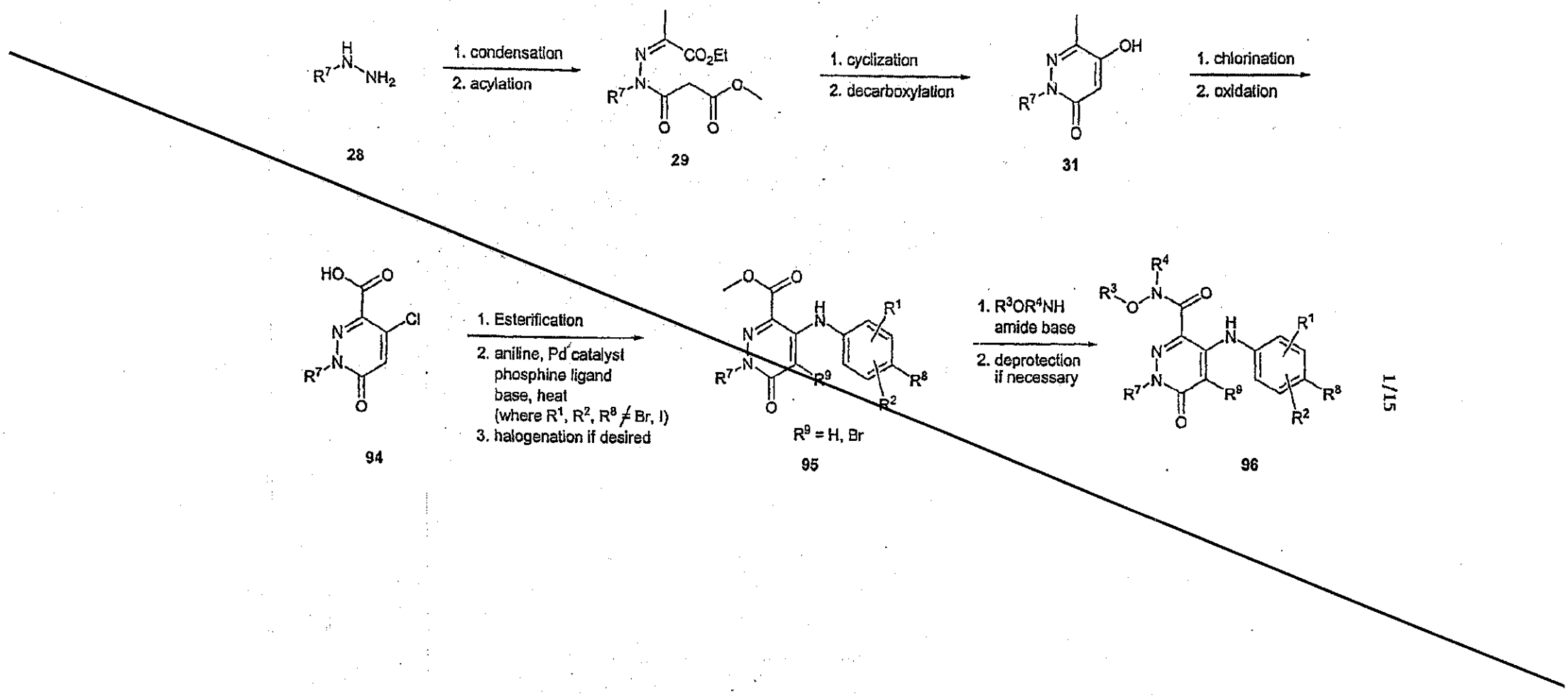

1. condensation
2. acylation
1. cyclization
2. decarboxylation
1. chlorination
2. oxidation
28
29
31
1. Esterification
2. aniline, Pd catalyst
phosphine ligand
base, heat
(where R1, R2, R8 ≠ Br, I)
3. halogenation if desired
R9 = H, Br
95
1. R3OR4NH
amide base
2. deprotection
if necessary
94
96

FIG. 1

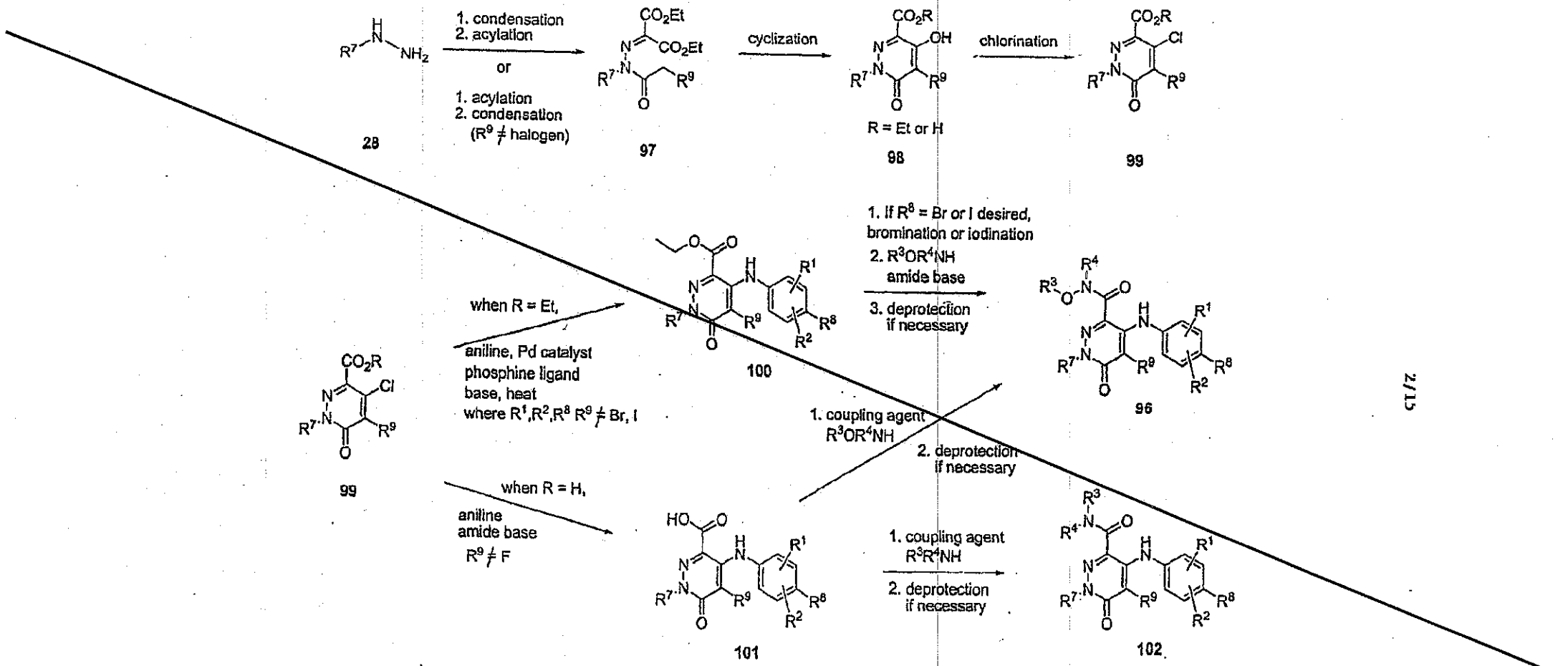

1. condensation
2. acylation
or
1. acylation
2. condensation
($R^9 \neq$ halogen)
28
97
cyclization
R = Et or H
98
chlorination
99
1. If R^8 = Br or I desired, bromination or iodination
2. R^3OR^4NH amide base
3. deprotection if necessary
96
when R = Et,
aniline, Pd catalyst
phosphine ligand
base, heat
where R^1, R^2, R^8 $R^9 \neq$ Br, I
100
99
when R = H,
aniline
amide base
$R^9 \neq$ F
1. coupling agent R^3OR^4NH
2. deprotection if necessary
101
1. coupling agent R^3R^4NH
2. deprotection if necessary
102

FIG. 2

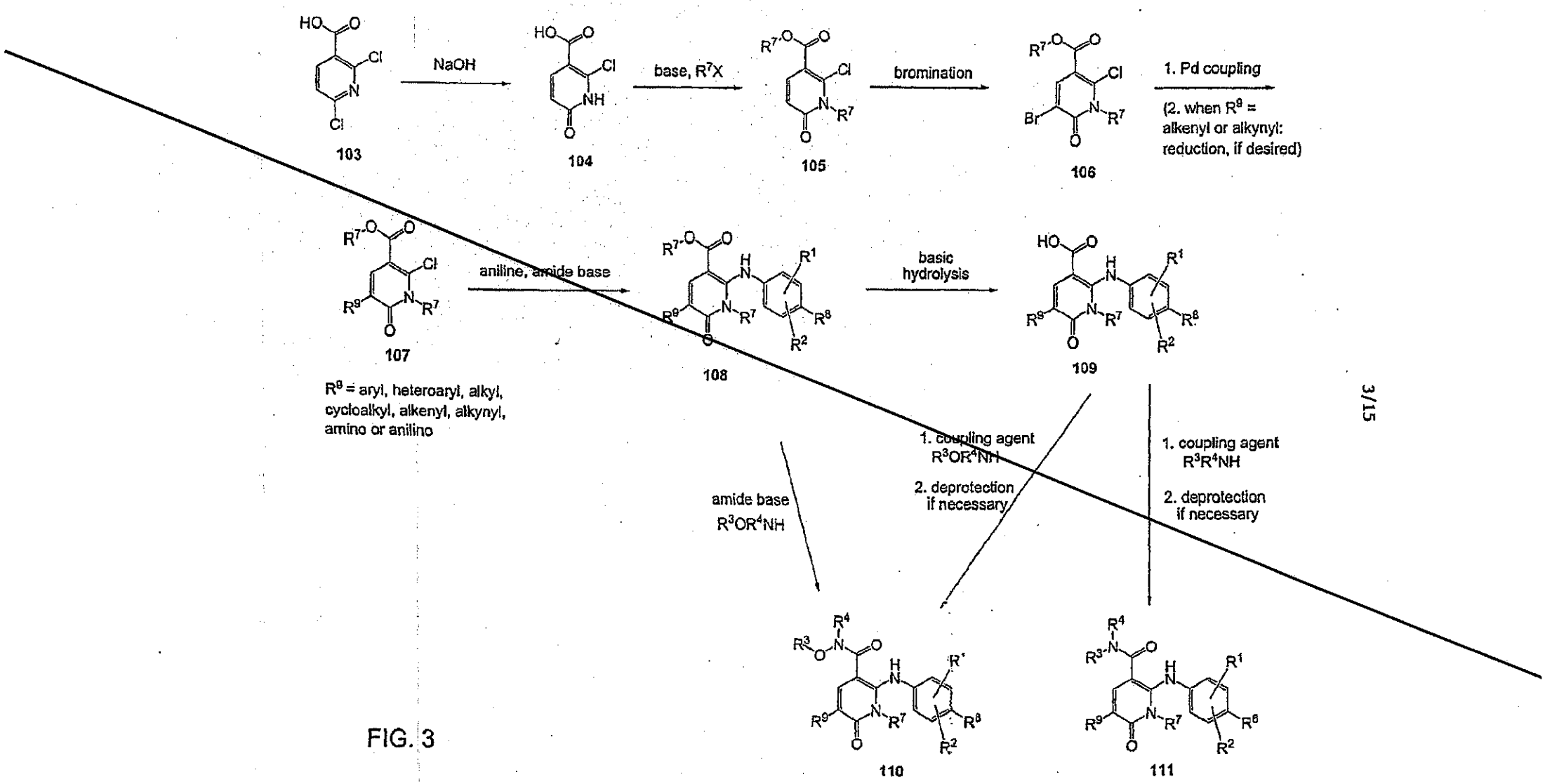

NaOH
base, R7X
bromination
1. Pd coupling
(2. when R9 = alkenyl or alkynyl: reduction, if desired)
103
104
105
106
aniline, amide base
basic hydrolysis
107
108
109
R9 = aryl, heteroaryl, alkyl, cycloalkyl, alkenyl, alkynyl, amino or anilino
1. coupling agent R3OR4NH
2. deprotection if necessary
amide base R3OR4NH
1. coupling agent R3R4NH
2. deprotection if necessary
110
111

FIG. 3

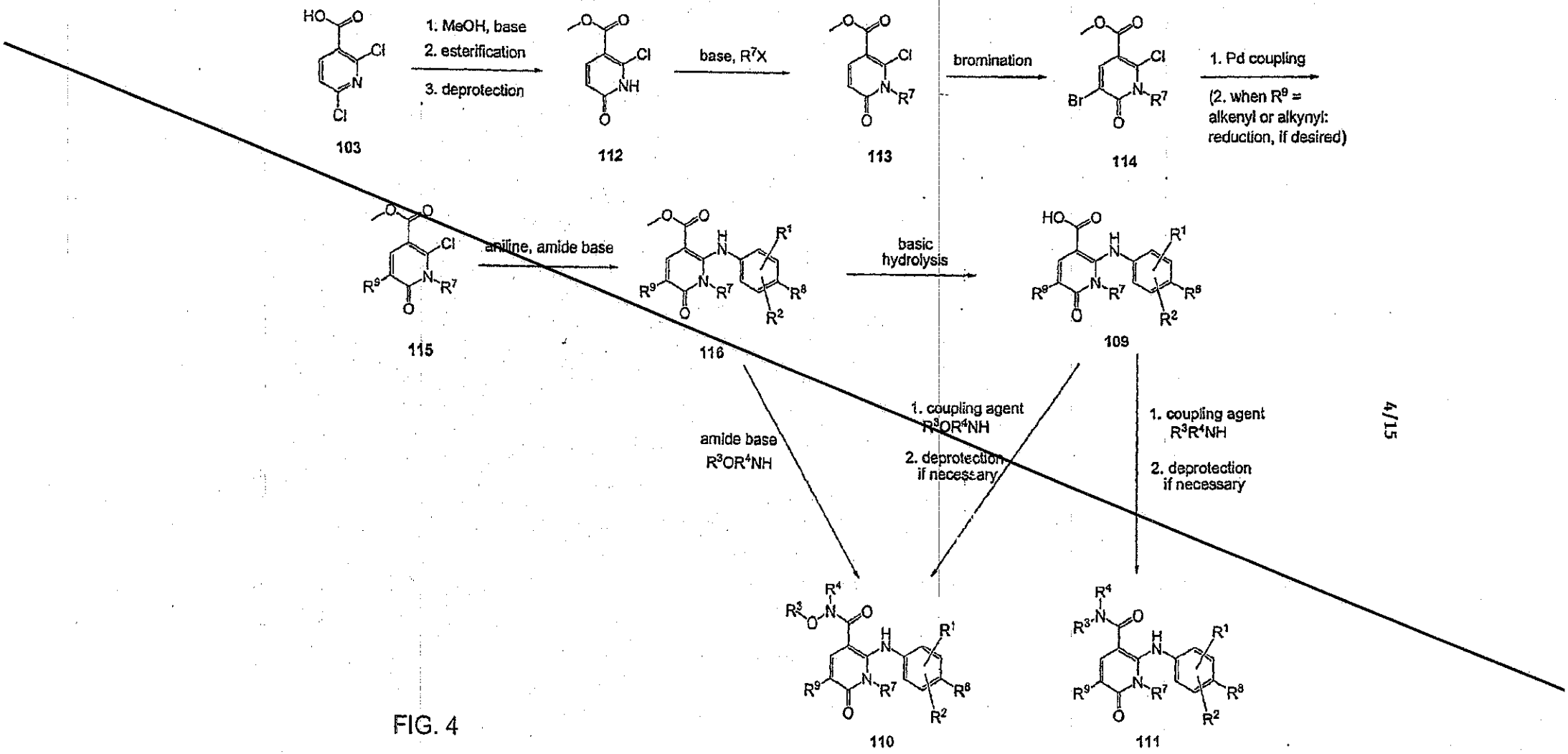

1. MeOH, base
2. esterification
3. deprotection
base, R7X
bromination
1. Pd coupling
(2. when R9 = alkenyl or alkynyl: reduction, if desired)
103
112
113
114
aniline, amide base
basic hydrolysis
115
116
109
amide base R3OR4NH
1. coupling agent R3OR4NH
2. deprotection if necessary
1. coupling agent R3R4NH
2. deprotection if necessary
110
111

FIG. 4

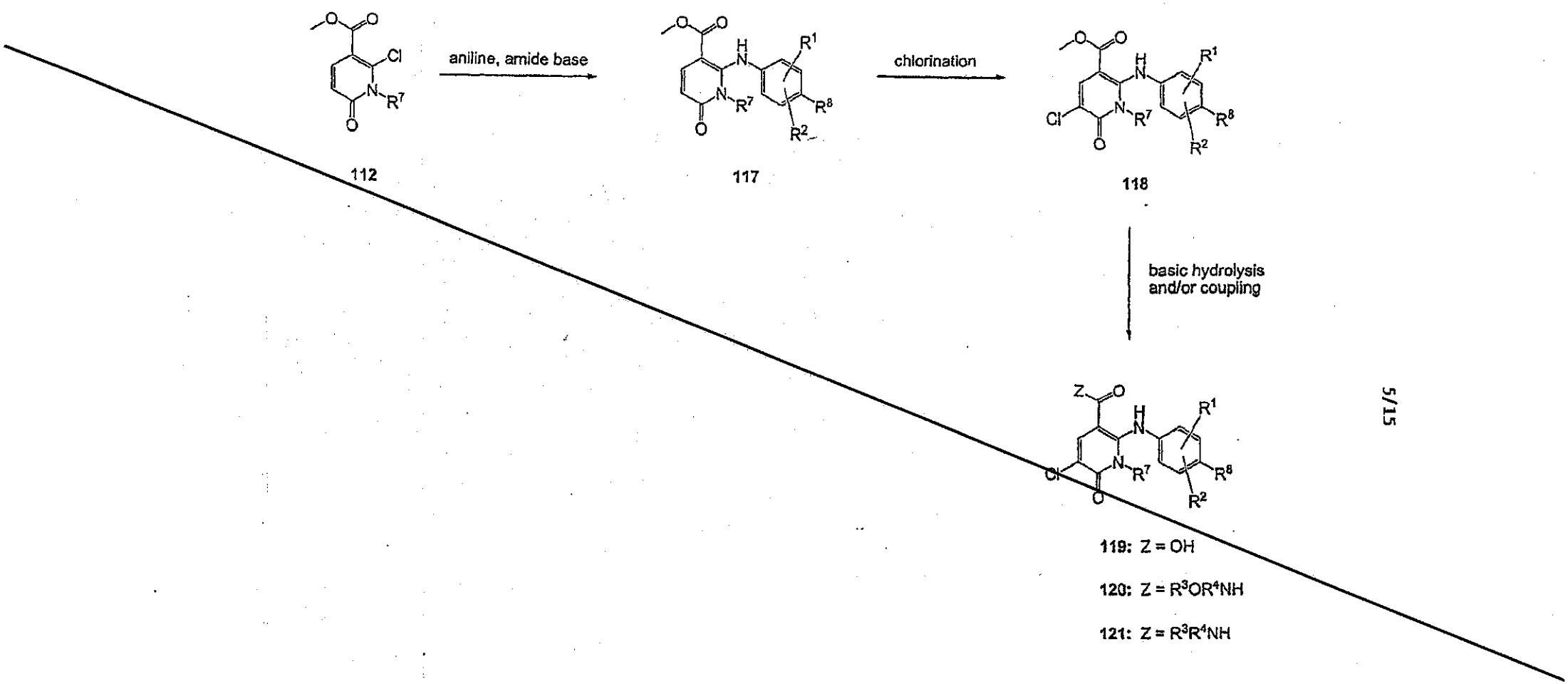

aniline, amide base
chlorination
basic hydrolysis
and/or coupling
112
117
118
119: Z = OH
120: Z = R3OR4NH
121: Z = R3R4NH

FIG. 5

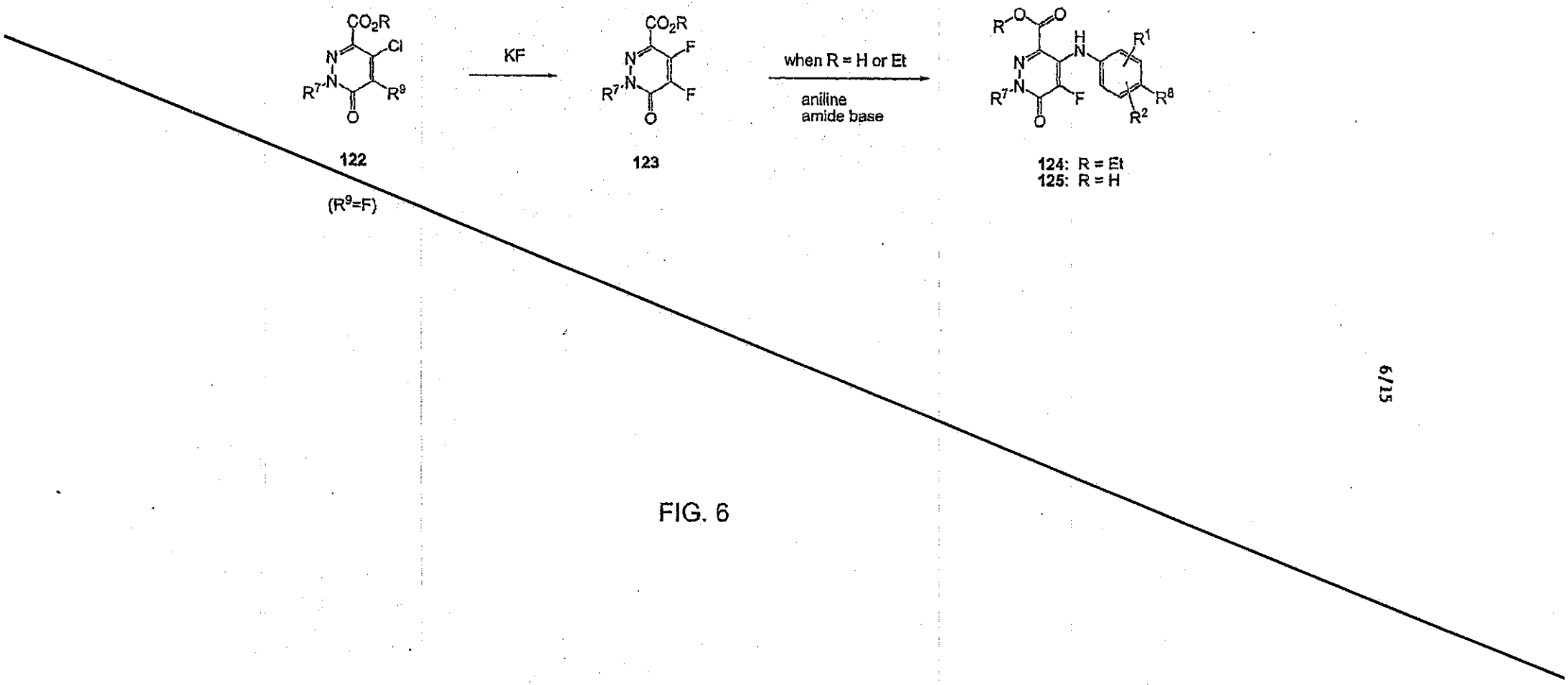

CO2R
Cl
N
R7-N
R9
O
122
(R9=F)
KF
CO2R
F
N
R7-N
F
O
123
when R = H or Et
aniline
amide base
R-O
O
H
N
R1
N
R7-N
F
R8
R2
O
124: R = Et
125: R = H

FIG. 6

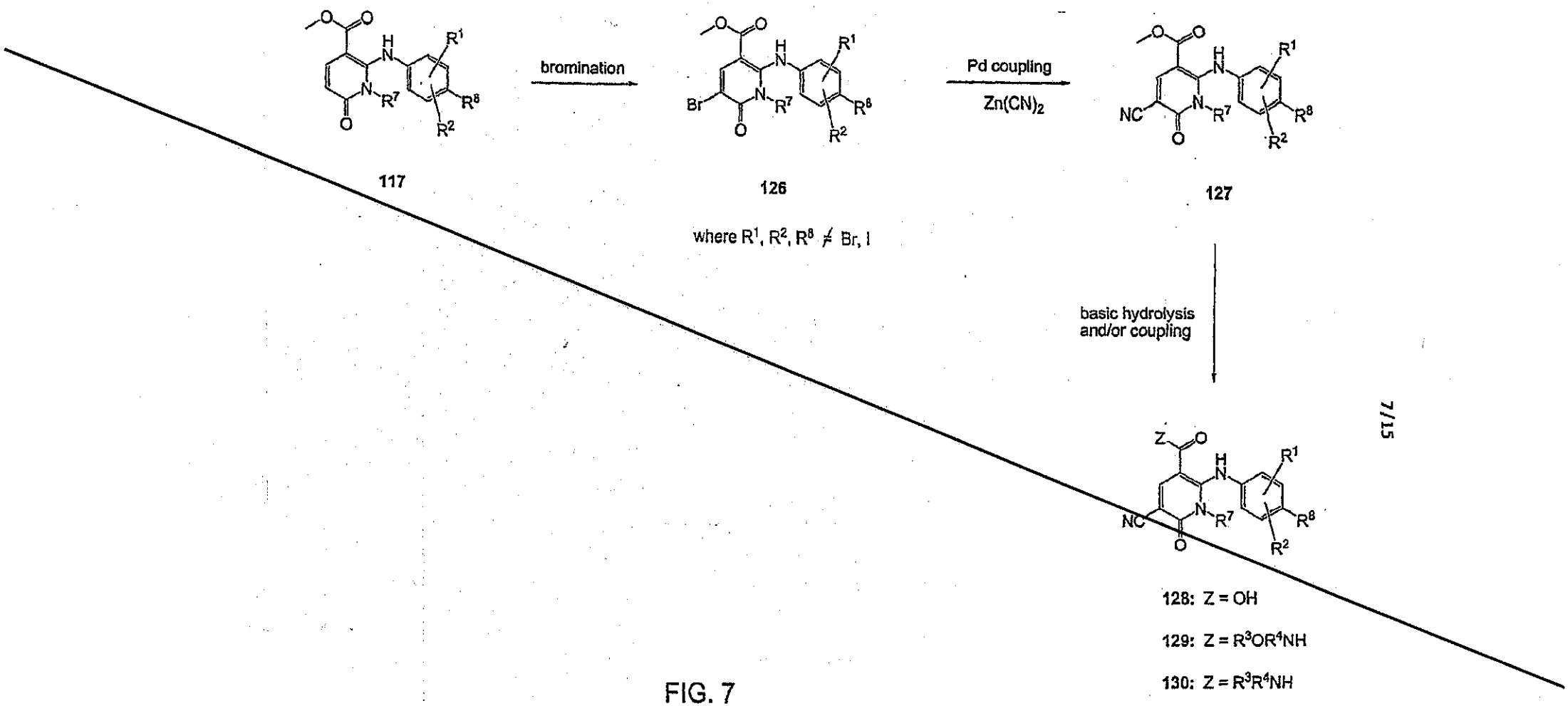

bromination
Pd coupling
Zn(CN)2
basic hydrolysis
and/or coupling
117
126
where R1, R2, R8 ≠ Br, I
127
128: Z = OH
129: Z = R3OR4NH
130: Z = R3R4NH

FIG. 7

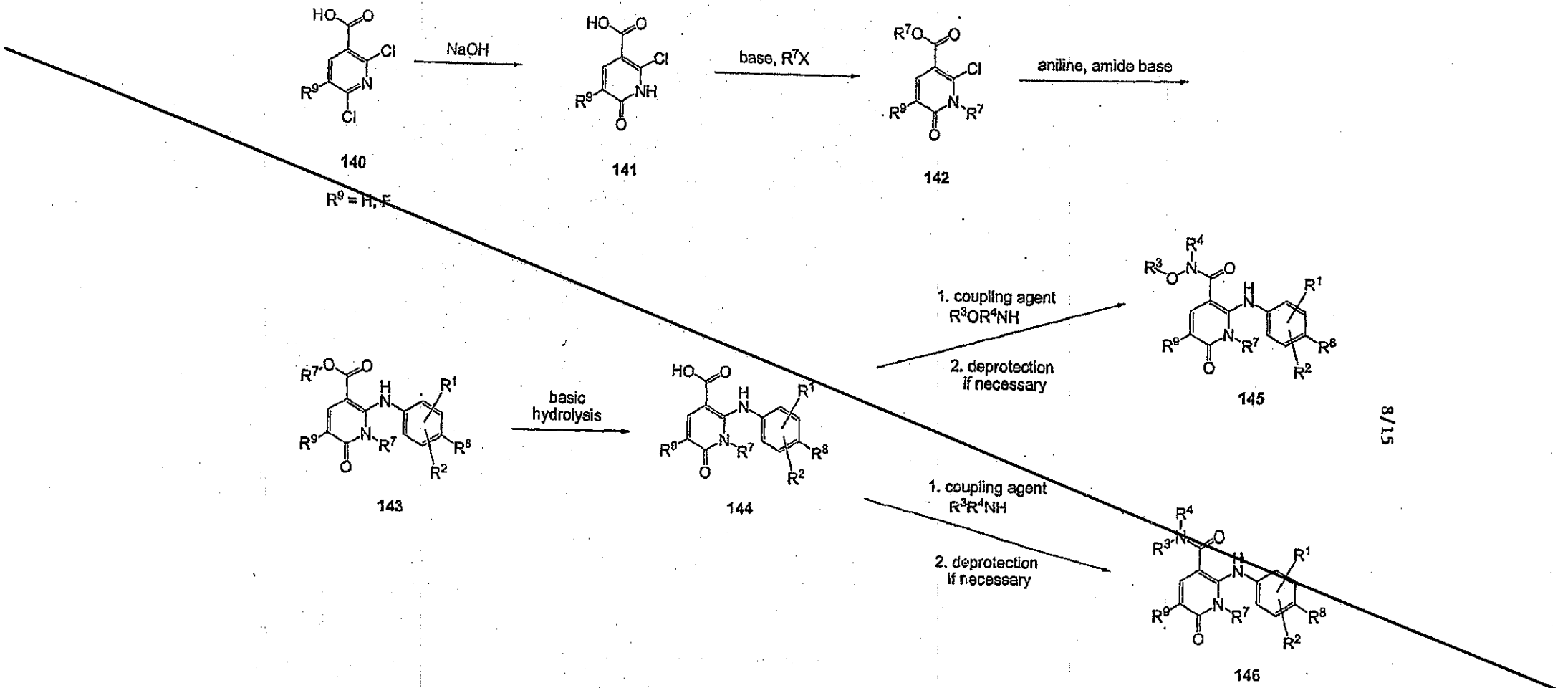

NaOH
base, R7X
aniline, amide base
140
R9 = H, F
141
142
1. coupling agent
R3OR4NH
2. deprotection
if necessary
145
basic
hydrolysis
143
144
1. coupling agent
R3R4NH
2. deprotection
if necessary
146

FIG. 8

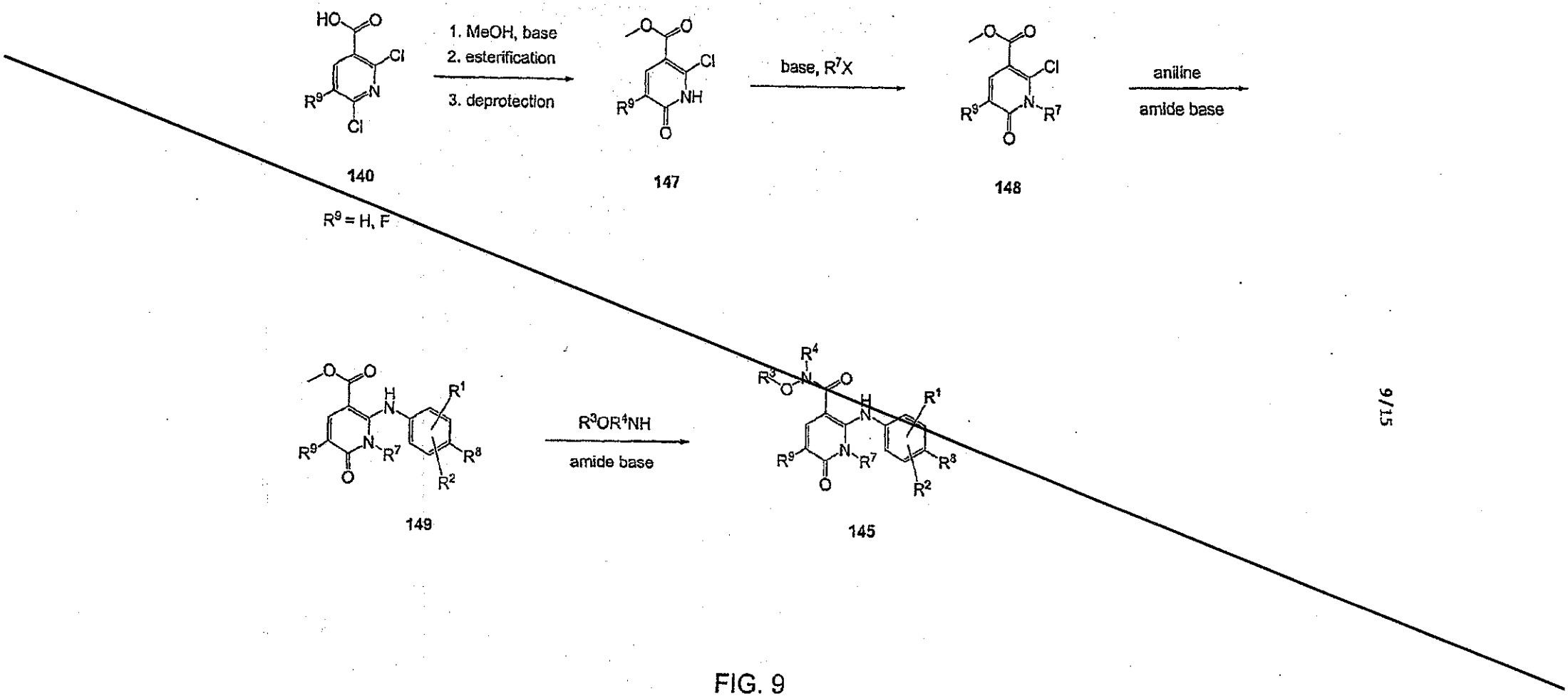

HO
O
Cl
N
R9
Cl
140
R9 = H, F
1. MeOH, base
2. esterification
3. deprotection
O
Cl
NH
R9
O
147
base, R7X
O
Cl
N
R7
R9
O
148
aniline
amide base
O
H
N
R1
N
R7
R9
R8
R2
O
149
R3OR4NH
amide base
R4
R3
O
N
O
H
N
R1
N
R7
R9
R8
R2
O
145

FIG. 9

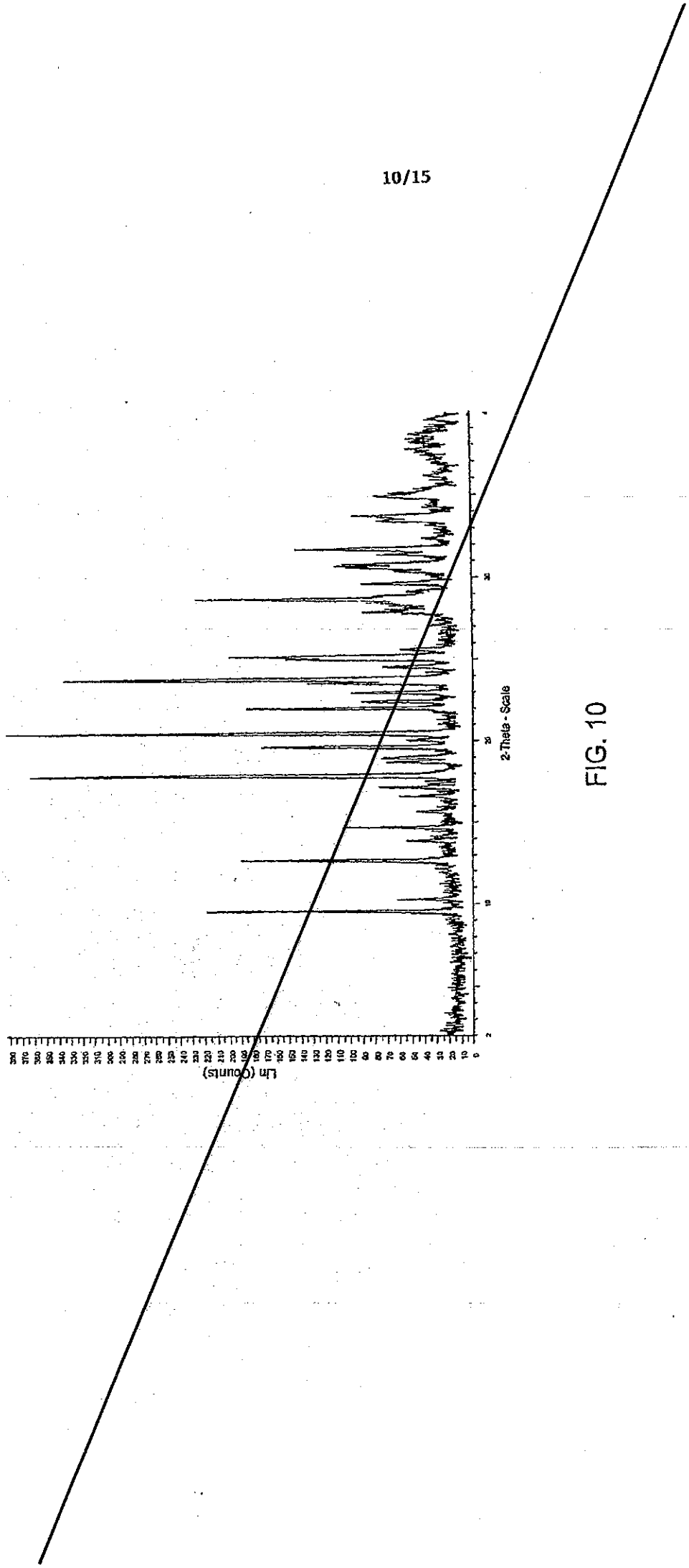


FIG. 10

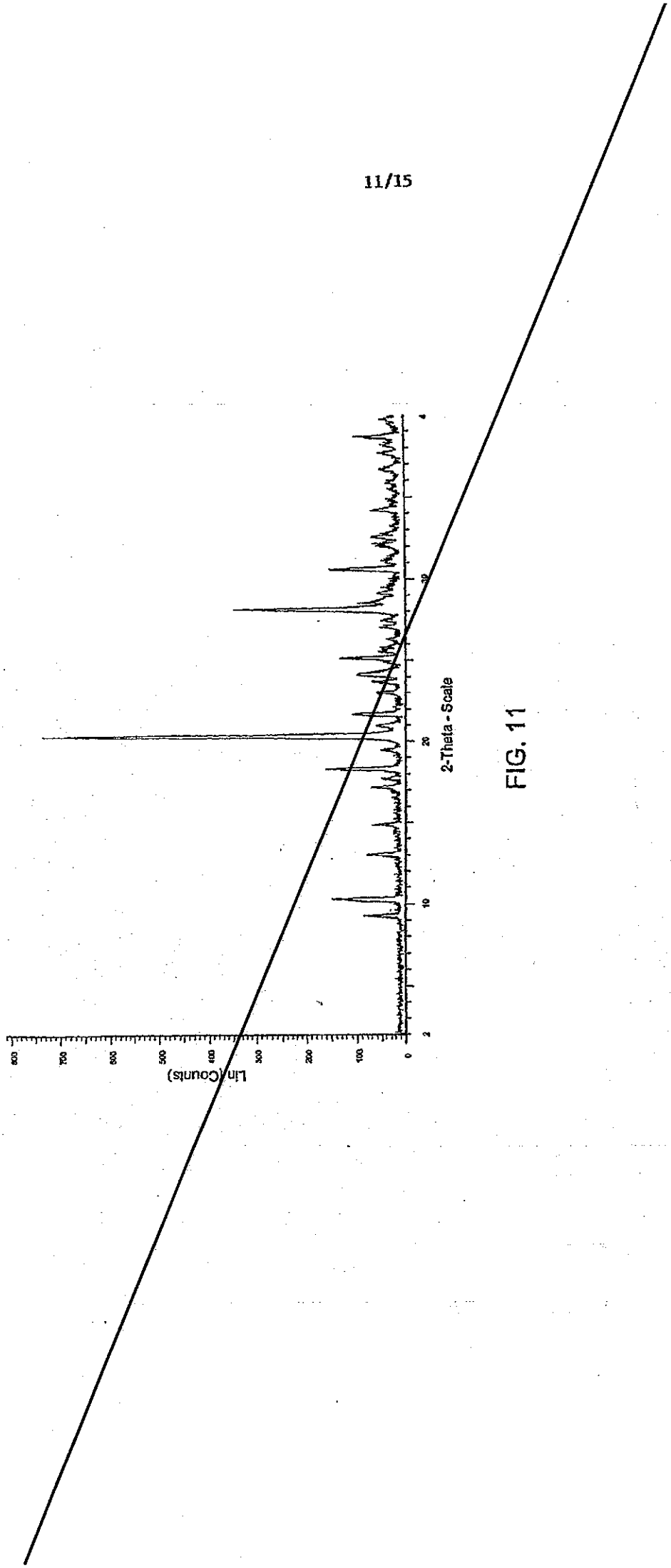


FIG. 11

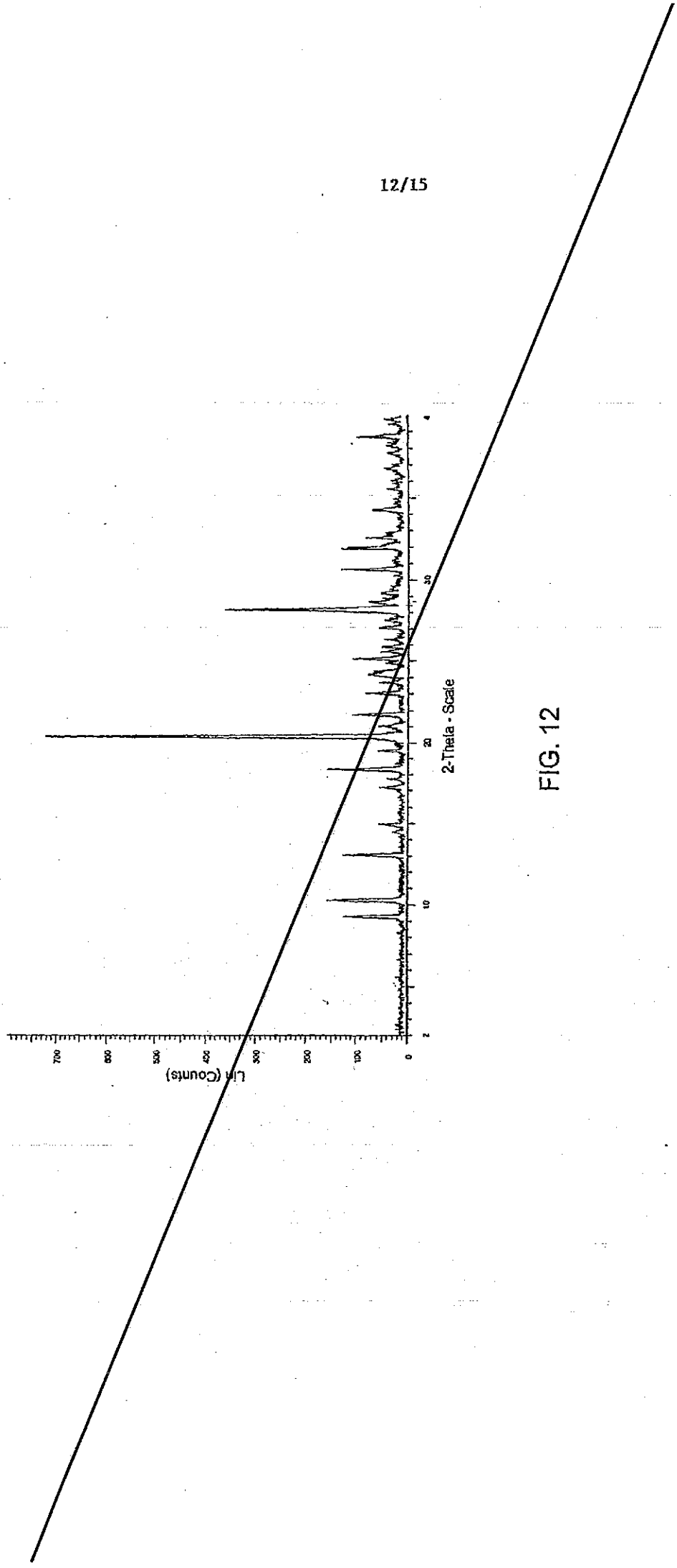


FIG. 12

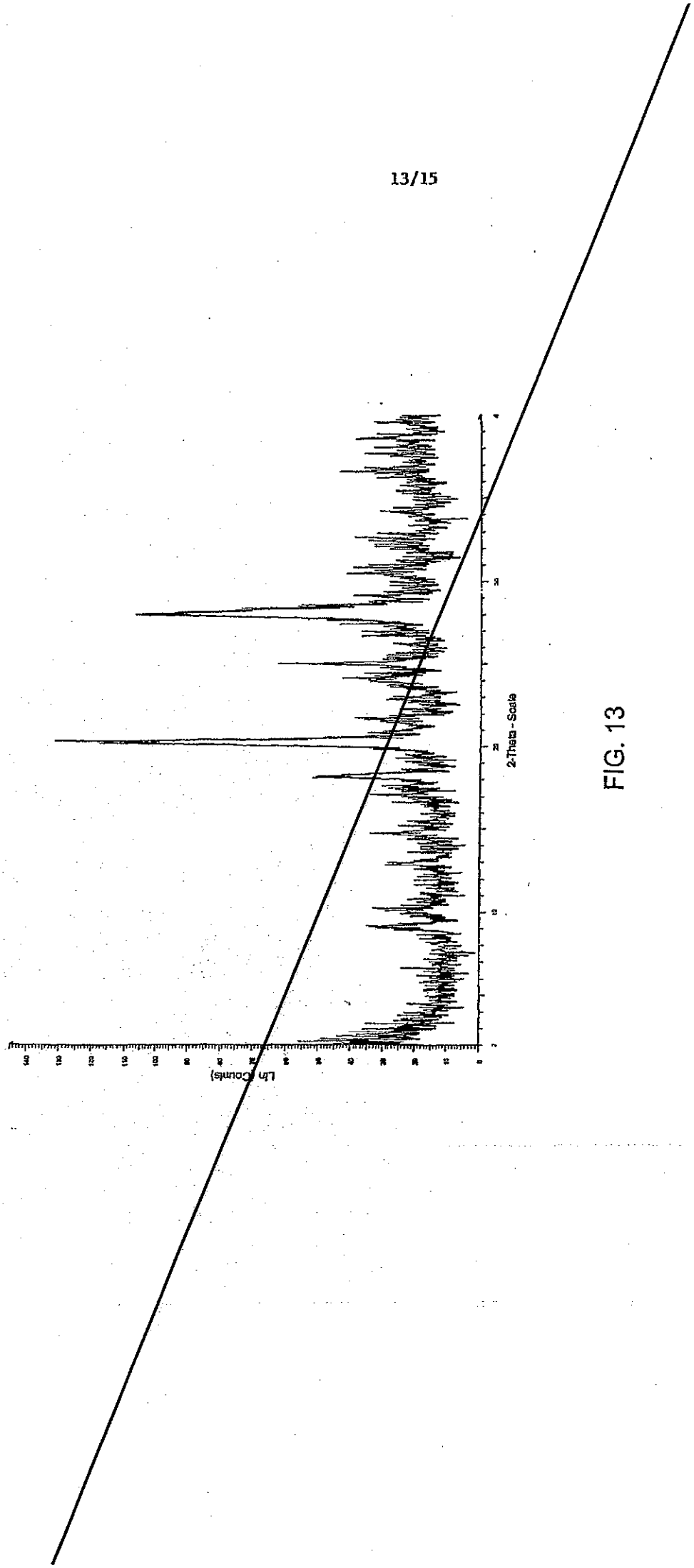


FIG. 13

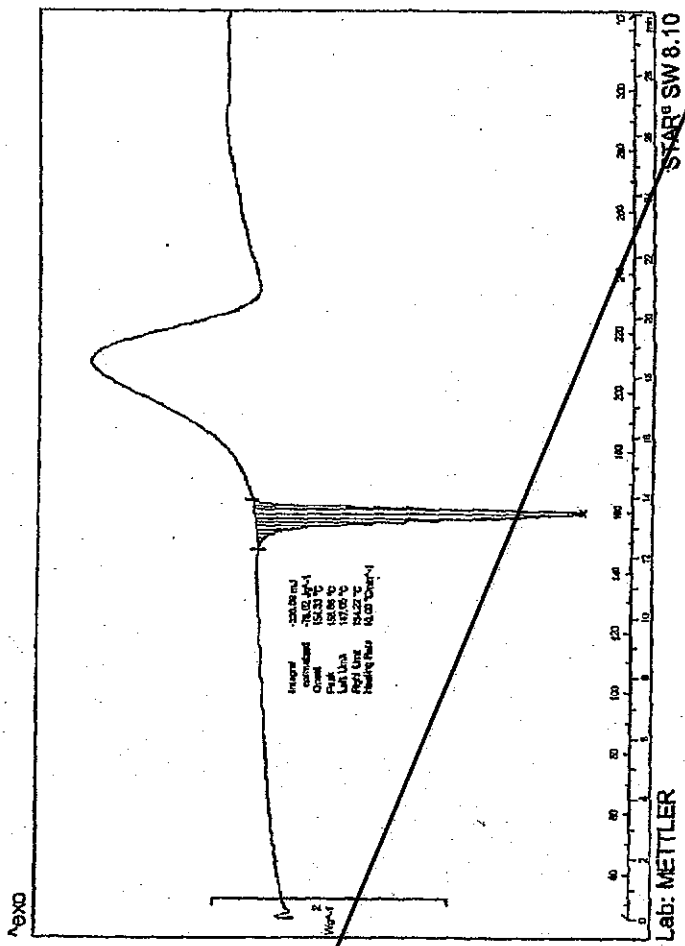


FIG. 14

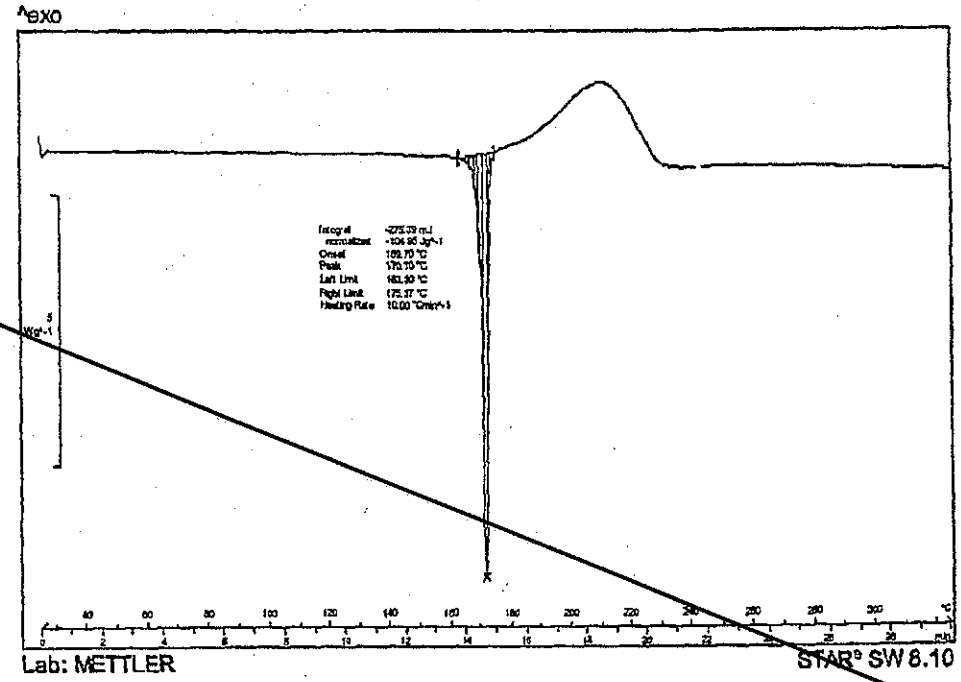


FIG. 15

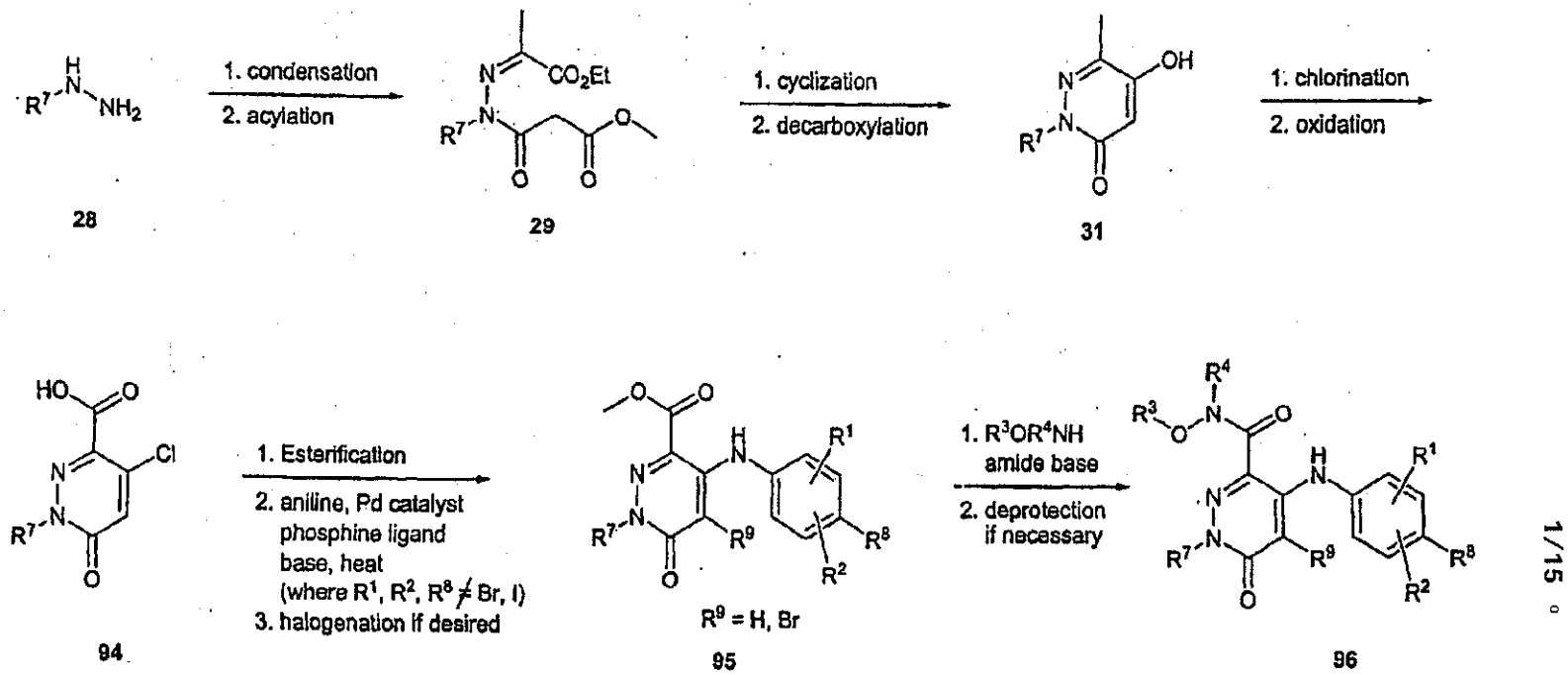

1. condensation
2. acylation
1. cyclization
2. decarboxylation
1. chlorination
2. oxidation
28
29
31
1. Esterification
2. aniline, Pd catalyst
phosphine ligand
base, heat
(where R1, R2, R8 ≠ Br, I)
3. halogenation if desired
R9 = H, Br
94
95
1. R3OR4NH
amide base
2. deprotection
if necessary
96

FIG. 1

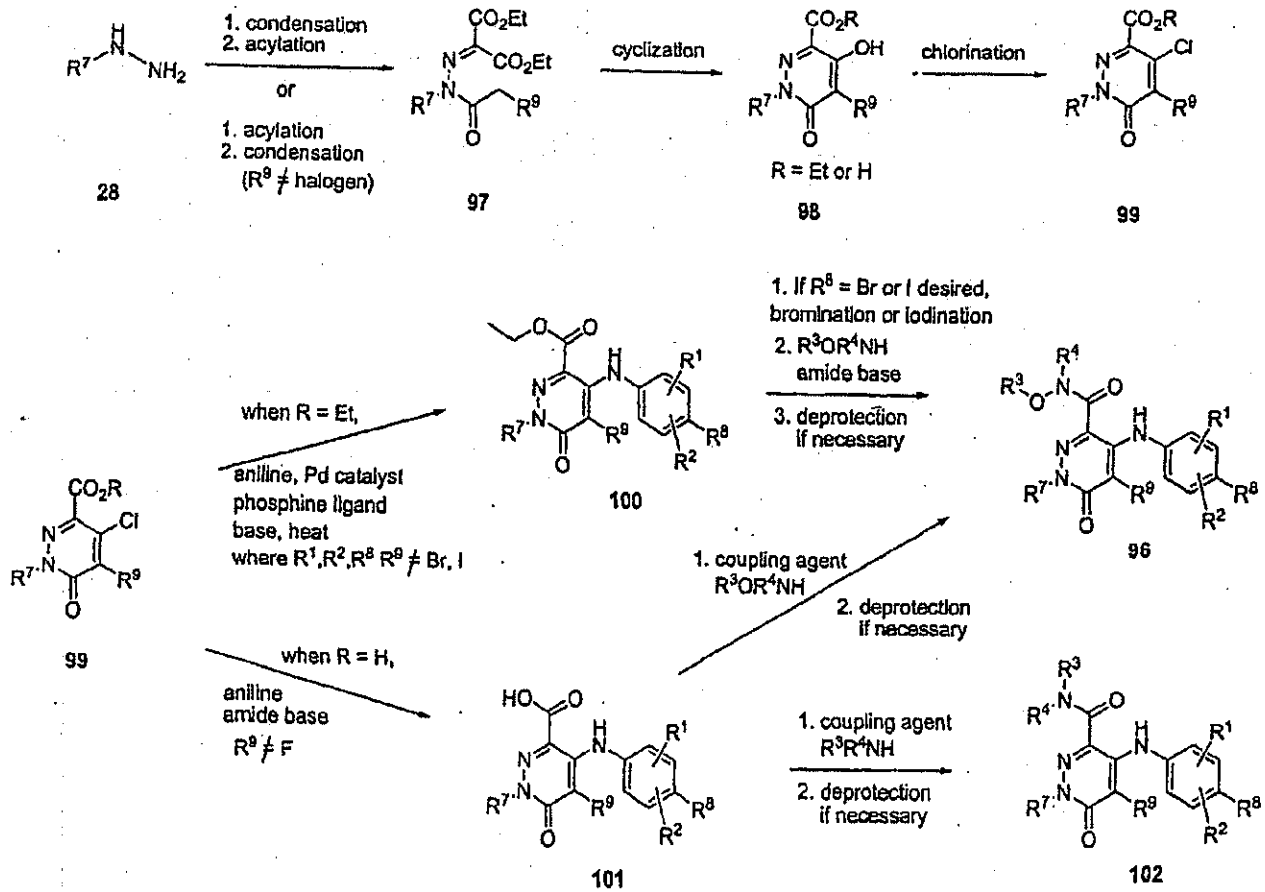

1. condensation
2. acylation
or
1. acylation
2. condensation
($R^9 \neq$ halogen)
cyclization
chlorination
28
97
98
99
R = Et or H
when R = Et,
aniline, Pd catalyst
phosphine ligand
base, heat
where R^1,R^2,R^8 $R^9 \neq$ Br, I
100
1. If R^8 = Br or I desired,
bromination or iodination
2. R^3OR^4NH
amide base
3. deprotection
if necessary
96
99
when R = H,
aniline
amide base
$R^9 \neq$ F
101
1. coupling agent
R^3OR^4NH
2. deprotection
if necessary
1. coupling agent
R^3R^4NH
2. deprotection
if necessary
102

FIG. 2

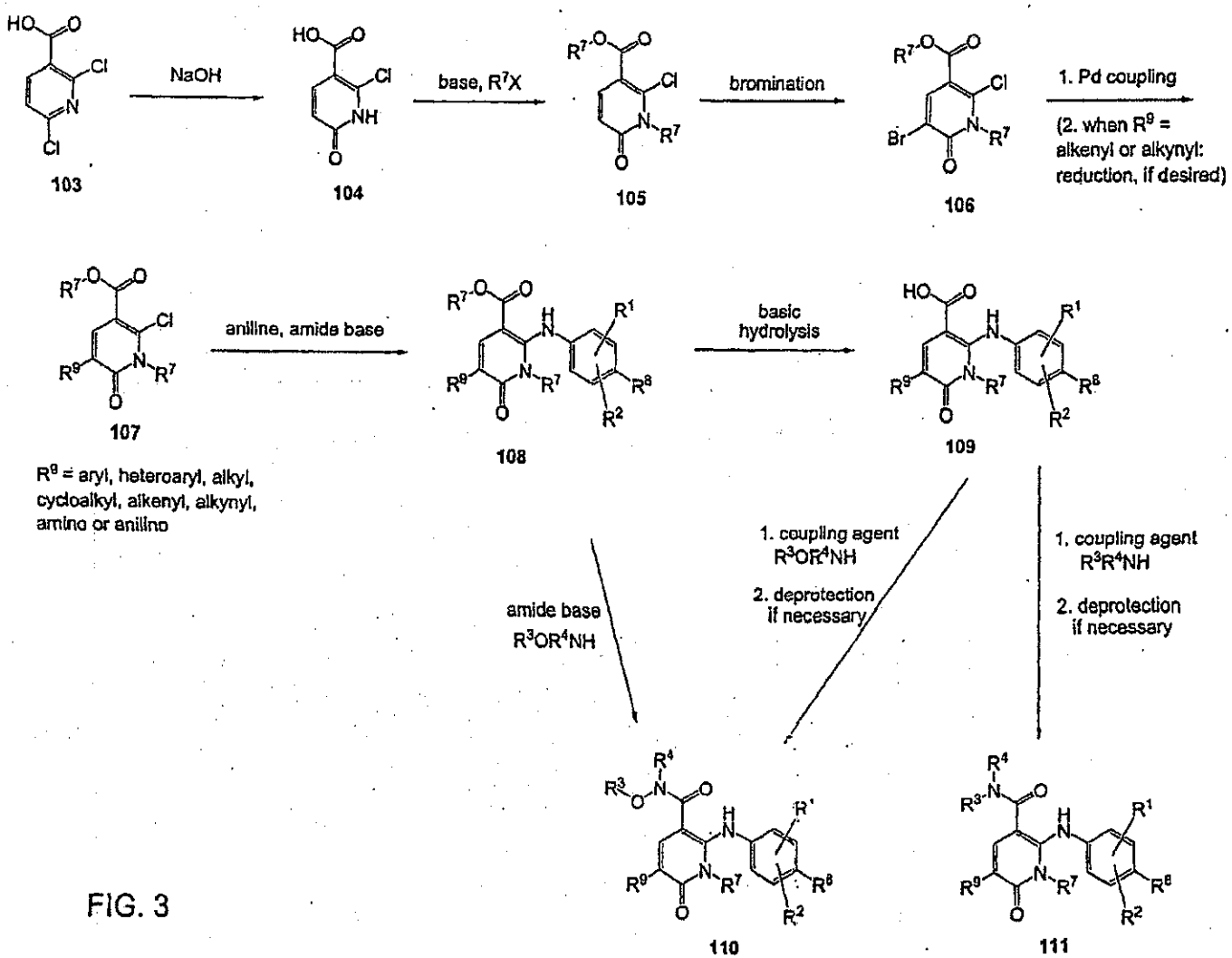

NaOH
base, R7X
bromination
1. Pd coupling
(2. when R9 = alkenyl or alkynyl: reduction, if desired)
103
104
105
106
aniline, amide base
basic hydrolysis
107
108
109
R9 = aryl, heteroaryl, alkyl, cycloalkyl, alkenyl, alkynyl, amino or anilino
1. coupling agent R3OR4NH
2. deprotection if necessary
amide base R3OR4NH
1. coupling agent R3R4NH
2. deprotection if necessary
110
111

FIG. 3

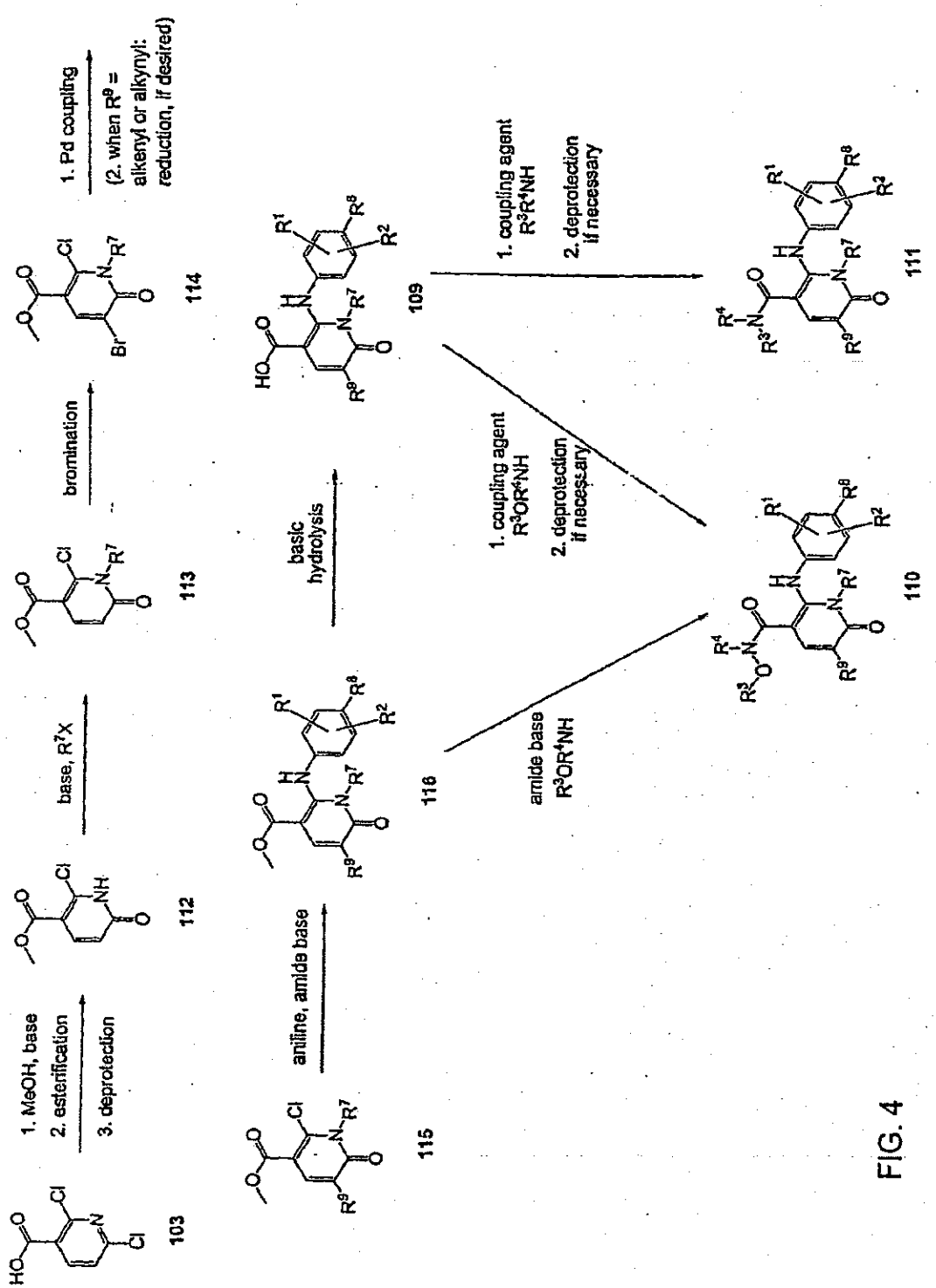

1. MeOH, base
2. esterification
3. deprotection
base, R7X
bromination
1. Pd coupling
(2. when R9 = alkenyl or alkynyl: reduction, if desired)
aniline, amide base
basic hydrolysis
1. coupling agent R3OR4NH
2. deprotection if necessary
amide base R3OR4NH
103
112
113
114
115
116
109
110
111

FIG. 4

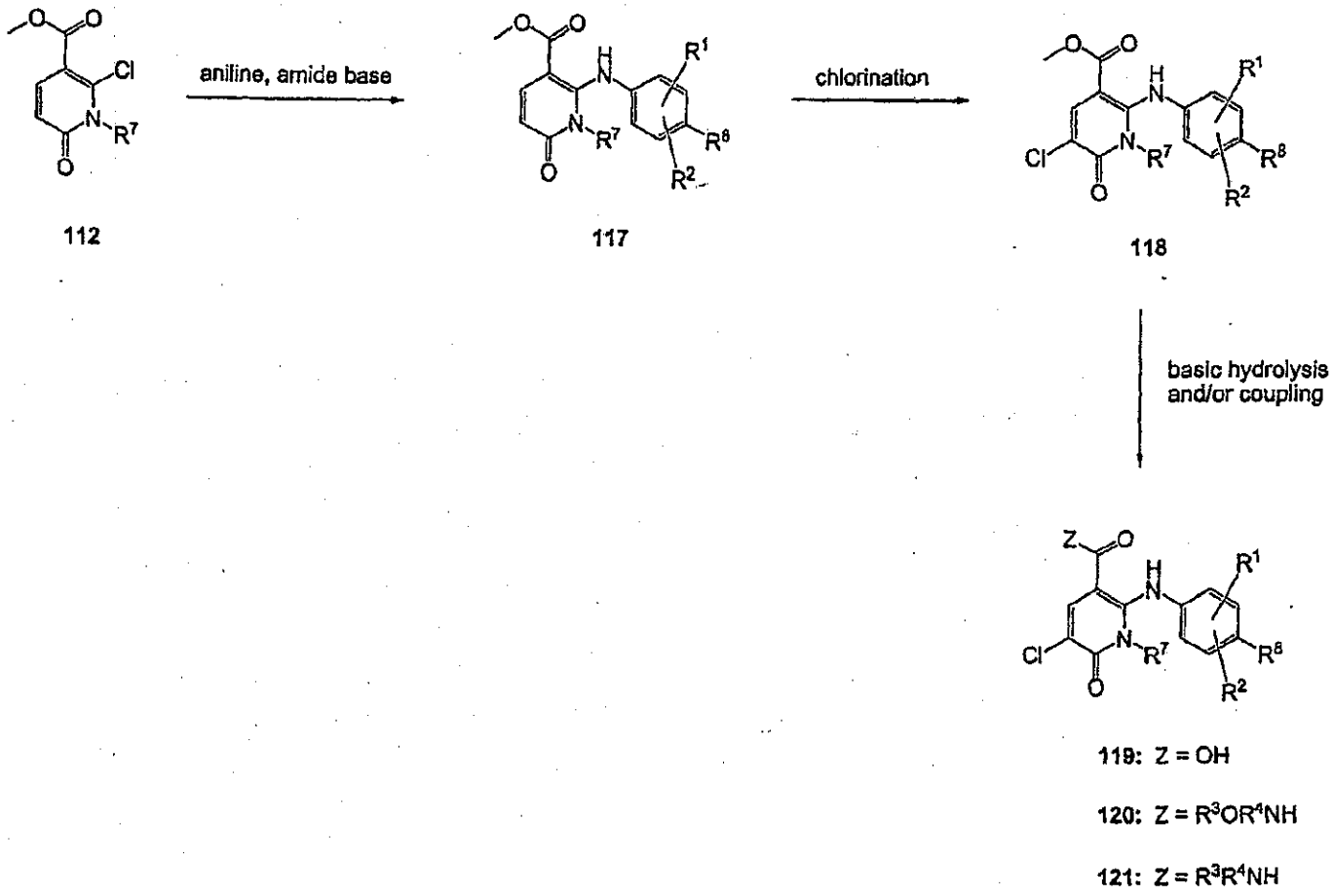
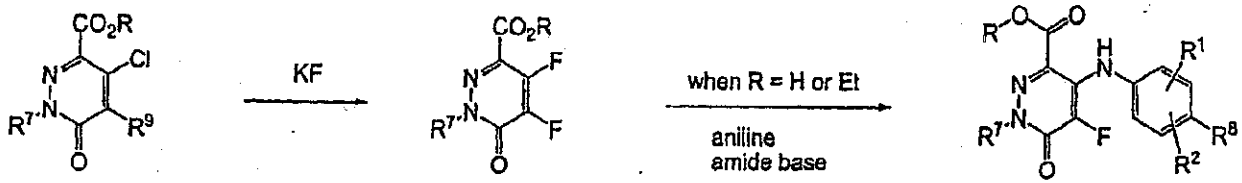

aniline, amide base
chlorination
basic hydrolysis
and/or coupling
112
117
118
119: Z = OH
120: Z = R3OR4NH
121: Z = R3R4NH

FIG. 5



122

(R^9=F)

123

124: R = Et
125: R = H

FIG. 6

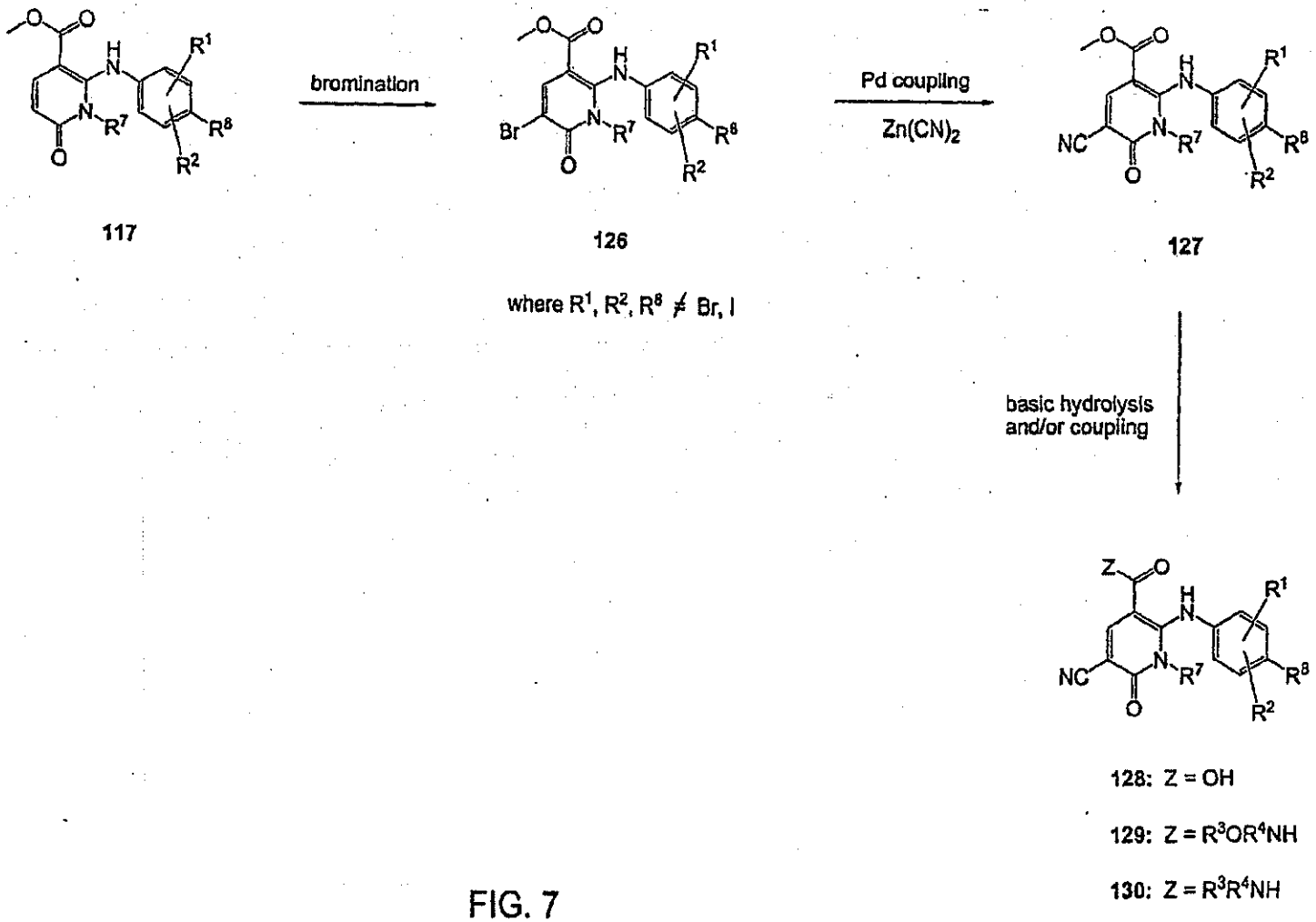

bromination
Pd coupling
Zn(CN)2
basic hydrolysis
and/or coupling
117
126
where R1, R2, R8 ≠ Br, I
127
128: Z = OH
129: Z = R3OR4NH
130: Z = R3R4NH

FIG. 7

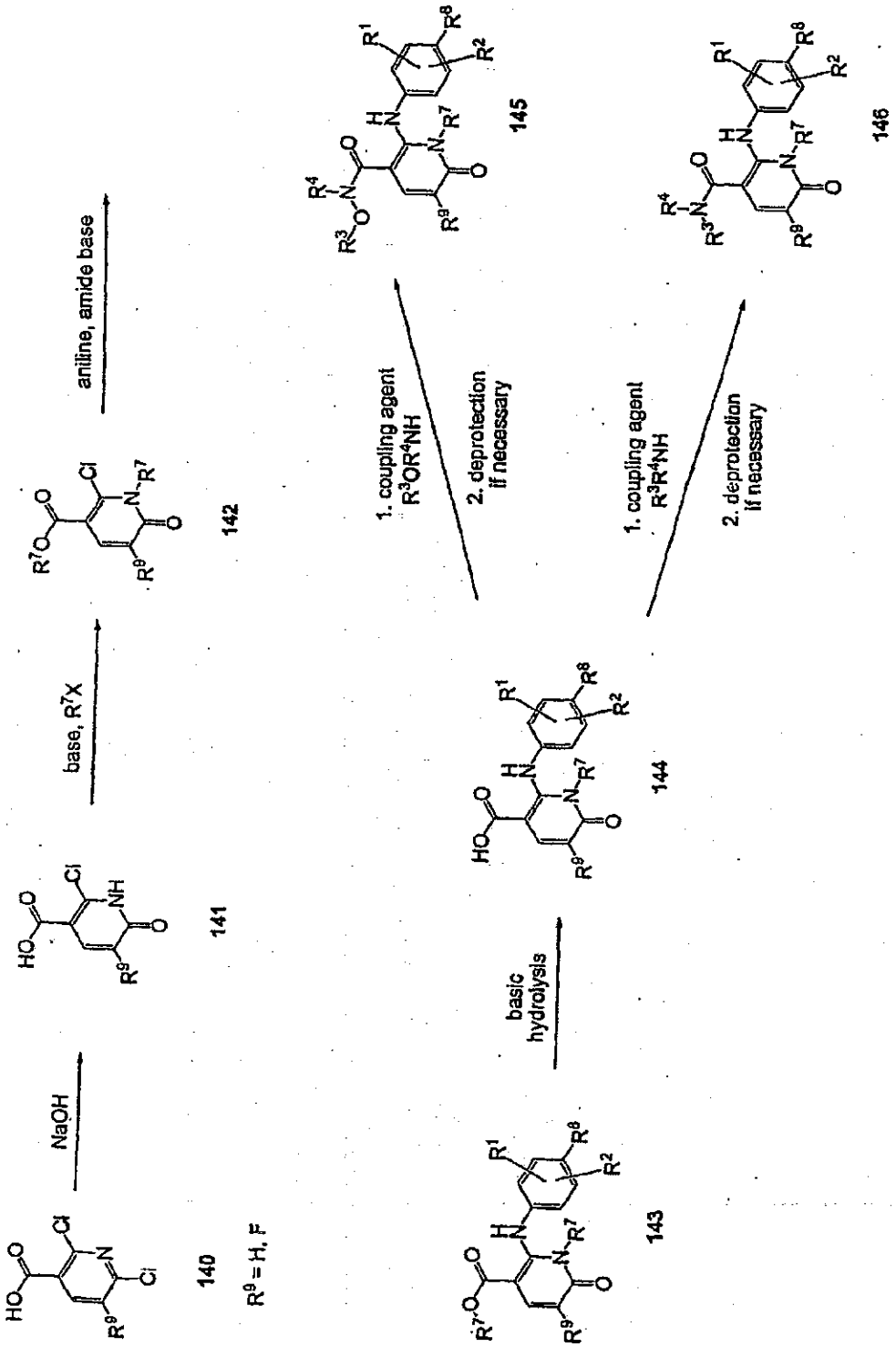
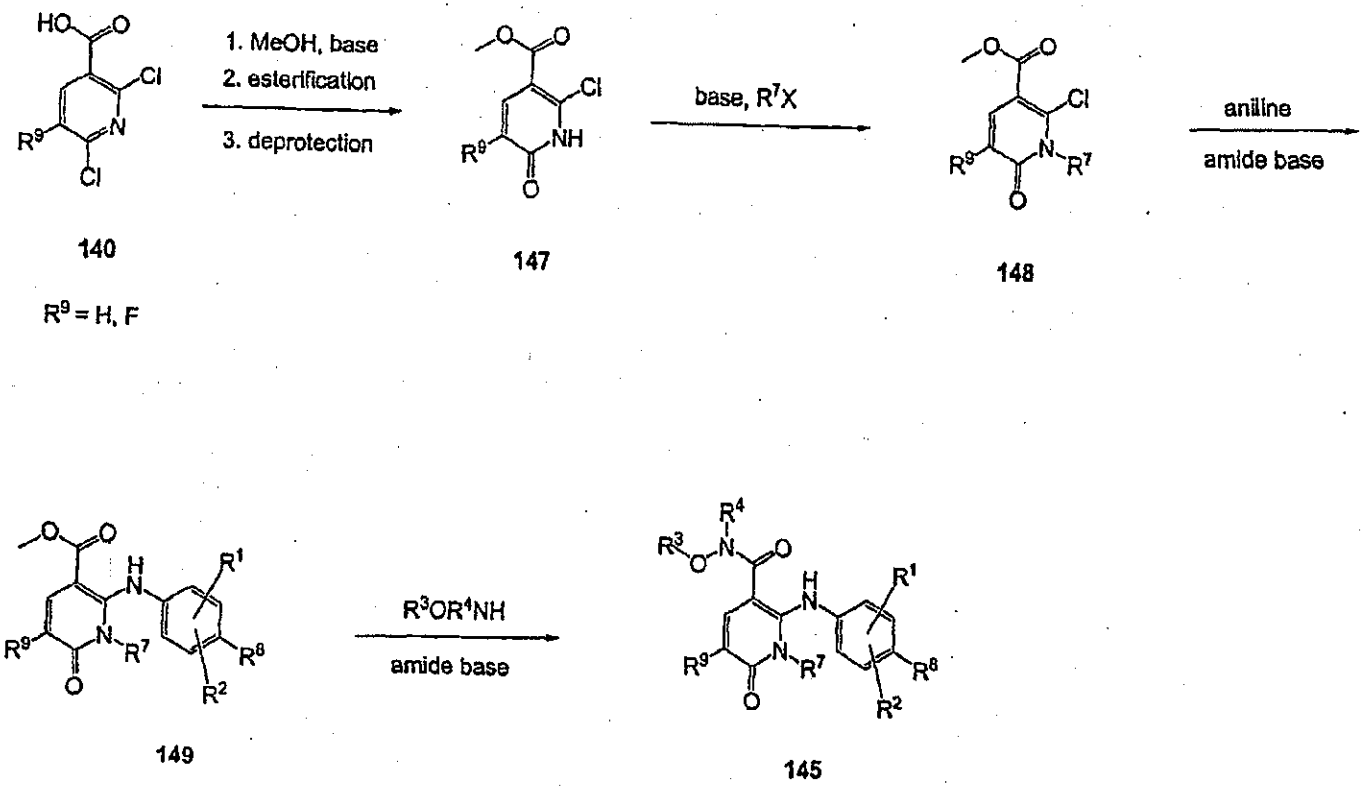

NaOH
base, R7X
aniline, amide base
basic hydrolysis
1. coupling agent R3OR4NH
2. deprotection if necessary
1. coupling agent R3R4NH
2. deprotection if necessary
140
141
142
143
144
145
146
R9 = H, F

FIG. 8



140

R^9 = H, F

147

148

149

145

FIG. 9

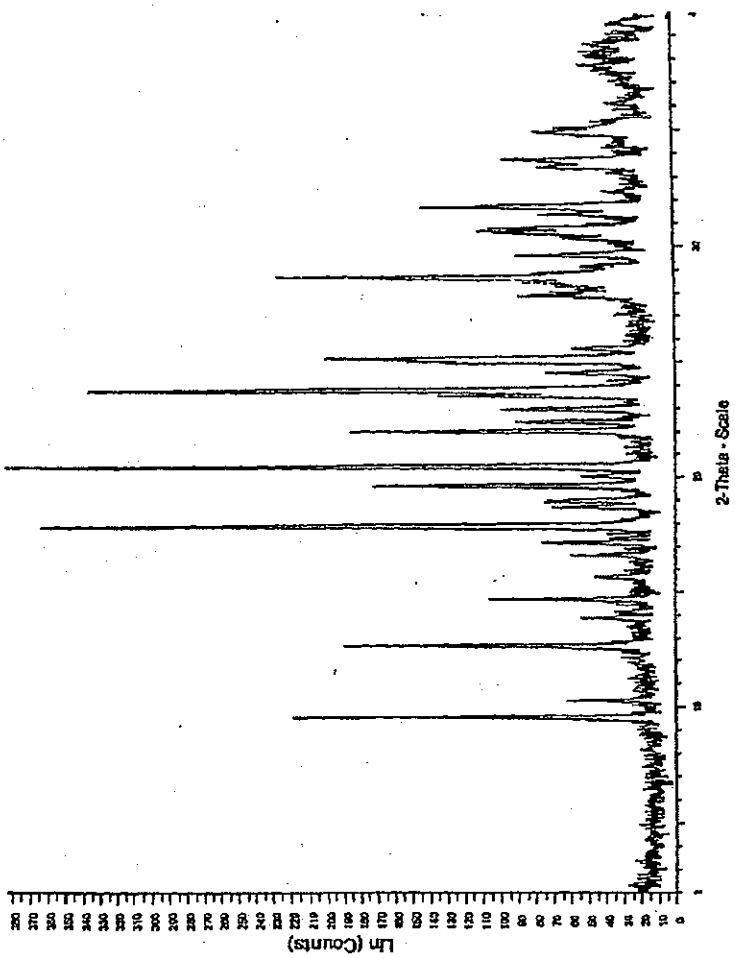


FIG. 10

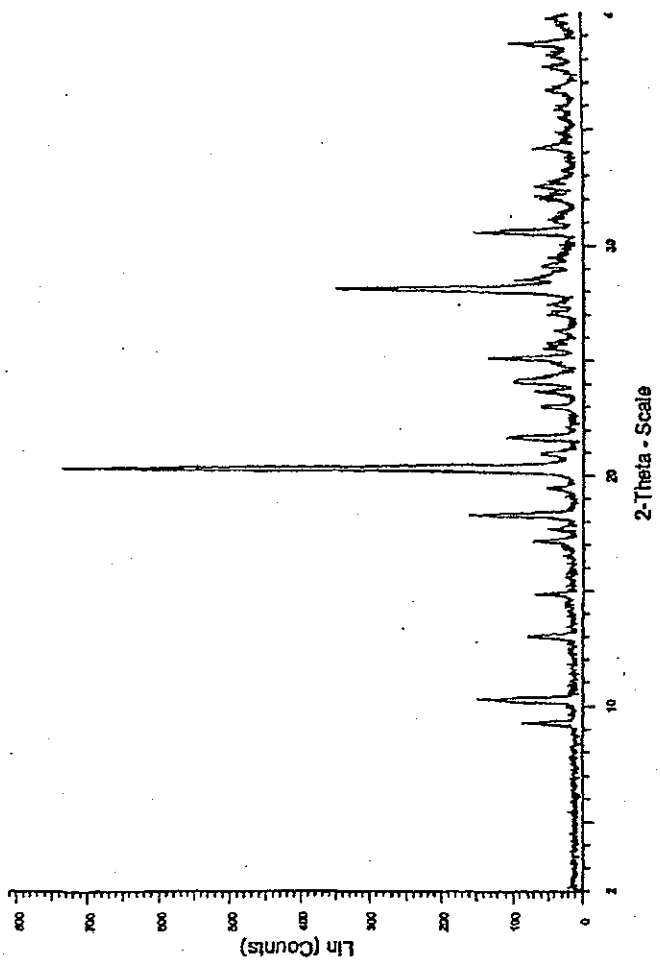


FIG. 11

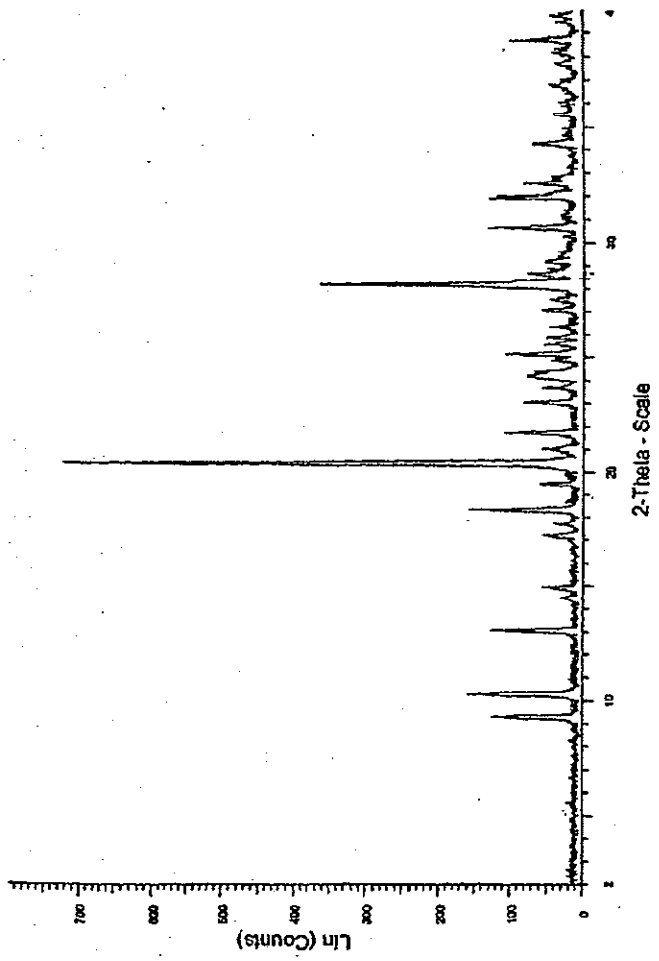

Lin (Counts)
0
100
200
300
400
500
600
700
2-Theta - Scale
2
10
20
30
4

FIG. 12

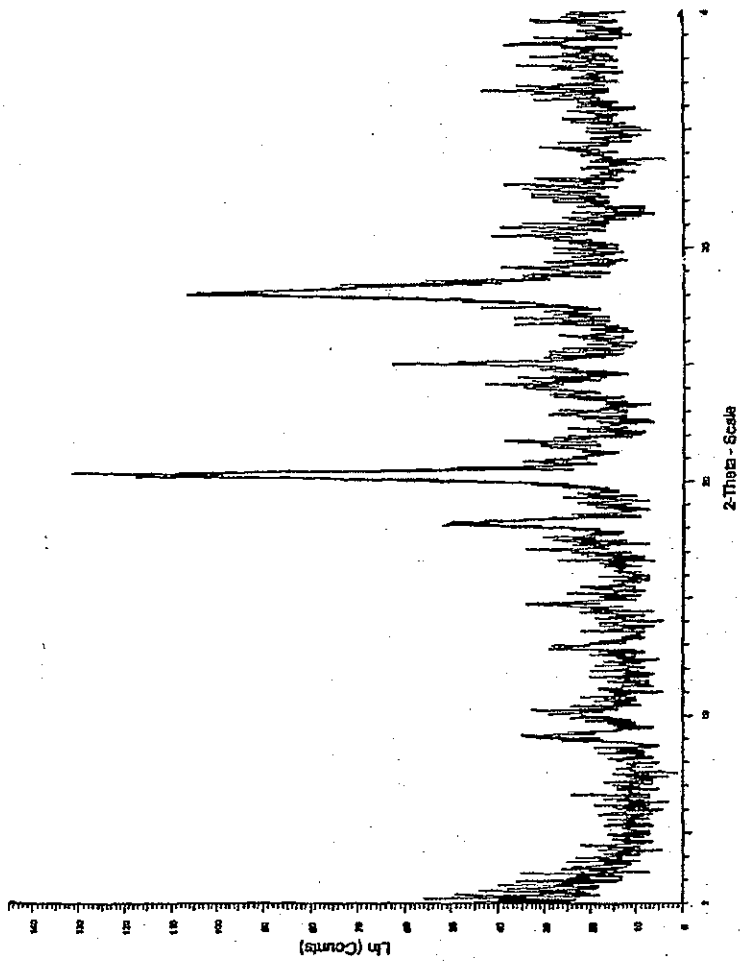


FIG. 13

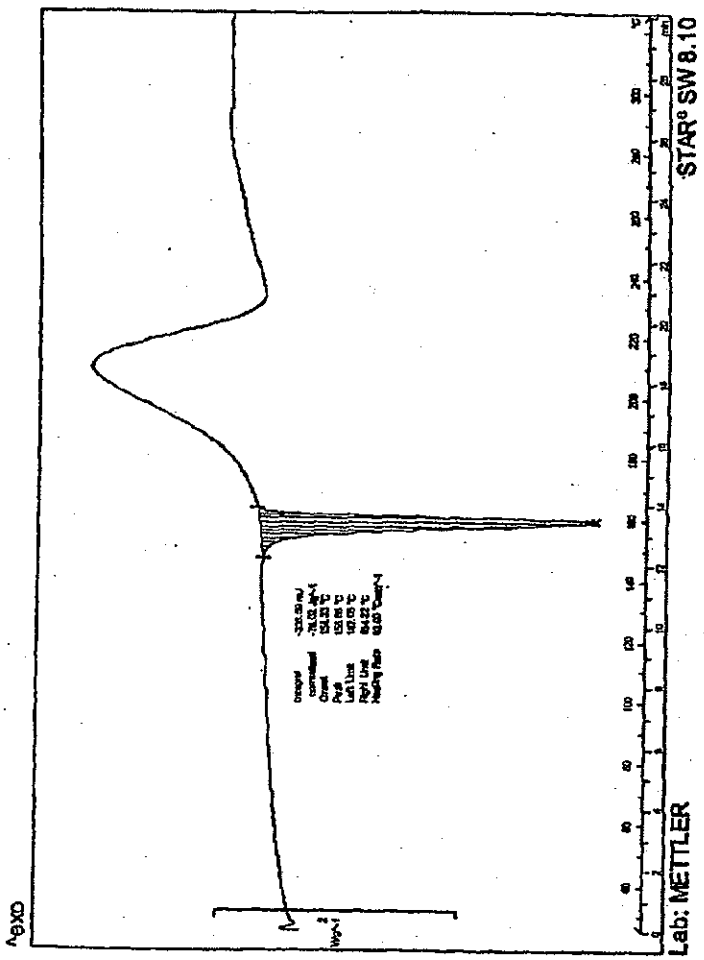


FIG. 14

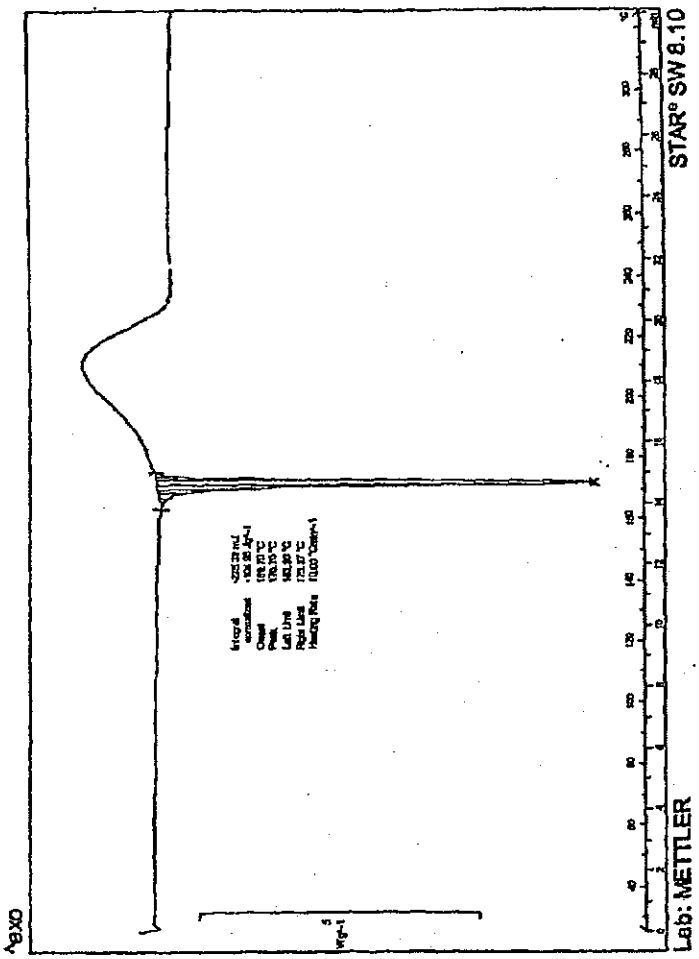


FIG. 15