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(54) Title: Cu-MEDIATED ANNULATION FOR THE PRODUCTION OF 1-AMINO-2-NAPHTHALENECARBOXYLIC ACID DERIVATIVES

(57) Abstract: Invention provides a cheaper and practical protocol for the construction of a wide variety of 1-Amino-2-naphthalene-carboxylic acid derivatives and their structural analogues that proceeds with high yields in a single step via intramolecular cascade cyano ene reaction.

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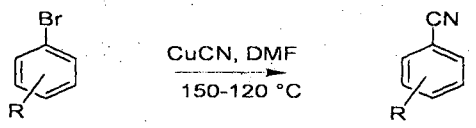
Cu-MEDIATED ANNULATION FOR THE PRODUCTION OF 1-AMINO-2-NAPHTHALENECARBOXYLIC ACID DERIVATIVES

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

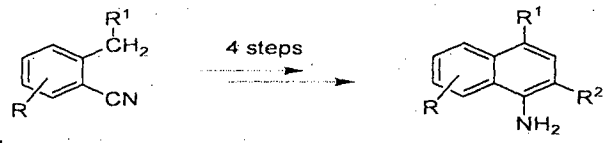
TECHNICAL FIELD OF THE INVENTION

This invention relates to cheaper and practical protocol for the construction of a wide variety of 1-Amino-2-naphthalenecarboxylic acid derivatives and their structural analogues that proceeds with high yields in a single step *via* intramolecular cascade cyano ene reaction.

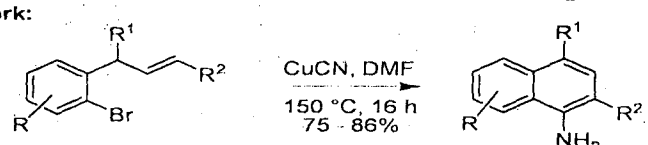
1) Rosenmund-von Braun Reaction:



2) Kobayashi et al:



3) This Work:



R = alkyl, alkoxy, halo, NO_2, CN, etc.
R^1 = H, alkyl, aryl
R^2 = CO_2Et, CO_2Me, $CO_2{}^tBu$, CN, $COCH_3$, SO_2Ph

Single Step

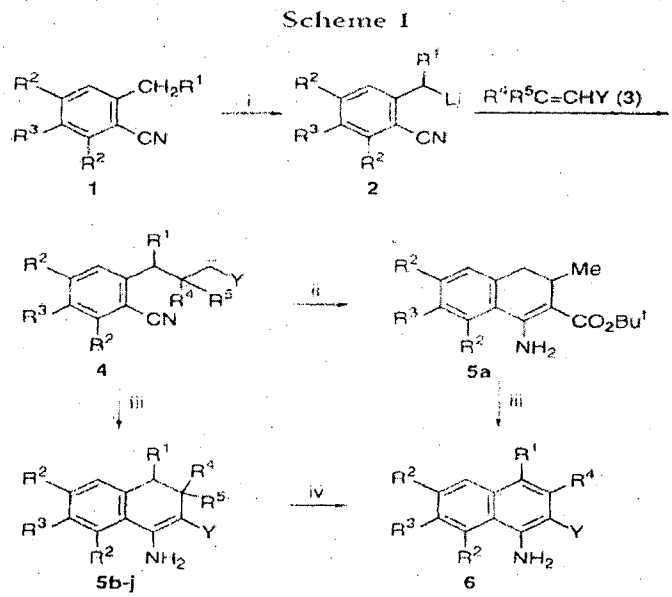
BACKGROUND AND PRIOR ART OF THE INVENTION

1-Amino-2-naphthalenecarboxylic Acid Derivatives are the intermediates of Dyes and Pigments useful in Peptide Synthesis. There is less literature available on preparation of 1-Amino-2-naphthalenecarboxylic Acid Derivatives. An article titled "Efficient Synthesis of 1-Amino-2-naphthalenecarboxylic Acid Derivatives via a Sequential Michael Addition/Enolate-Nitrile Coupling Route and Its Application to Facile Preparation of 9-Amino Analogues of Arylnaphthofuranone Lignans" by Kazuhiro Kobayashi et al, published in J.Org. Chem 1997, 62, 664-668, wherein, a

method for the general preparation of 1-amino-2-naphthalenecarboxylates and nitriles, which is based on the tandem Michael addition/enolate-nitrile coupling reaction between alpha-lithio derivatives of 2-alkylbenzonitriles and alpha-beta unsaturated carboxylic acid derivatives is described.

The reaction of 2-(alpha-lithioalkyl)benzonitriles, generated in situ by treatment of 2-alkylbenzonitriles with LDA in diglyme, with alpha-beta unsaturated carboxylates and nitriles produced 1-amino-3,4-dihydro-2-naphthalenecarboxylates and carbonitriles in 54-98% yields through Michael addition of the lithio nitriles to alpha-beta unsaturated carboxylic acid derivatives, followed by zinc iodide-promoted intra molecular enolate-nitrile coupling of the resulting enolate intermediates. The dihydronaphthalenecarboxylic acid derivatives were converted to the corresponding 1-amino-2-naphthalenecarboxylic acid derivatives in 43-99% yields on dehydrogenation with palladium on activated carbon in refluxing p-cymene. The synthesis is depicted in scheme 1 below.

Scheme 1



Reagents and conditions: i, 2LDA, THF, -78 °C; ii, -78 °C to r.t.; iii, ZnI_2, -78 °C to r.t.; iv, 10% Pd/C, *p*-cymene, reflux

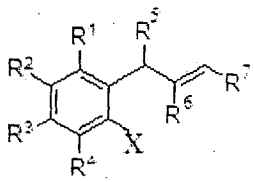
The process disclosed in the above prior art involves multiple steps and hence not feasible on industrial scale. Also, the process requires consumption of large quantities of hazardous chemicals with longer reaction time with less efficiency and narrow substrate scope.

OBJECTS OF THE INVENTION

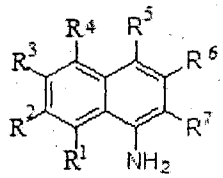
Main object of the present invention is to provide an effective synthesis for the preparation of 1-Amino-2-naphthalenecarboxylic acid and its derivatives with quantitative yields.

SUMMARY OF THE INVENTION

Accordingly, present invention provides a one pot process for the preparation of compound of formula (A) and their structural analogues comprising reacting compound of formula (B) with CuCN in solvent at a temperature in the range of 145°-155°C for time period in the range of 10 to12 hours;



Formula (B)



Formula (A)

Wherein,

R^1 ,R^2 ,R^3, R^4 are selected independently from the group consitsitng of hydrogen, alkyl, alkoxy, halo, NO_2 or CN;

R^5 is slected independently from the group consitsitng of H, CH_3, C_2H_5, Ph or $CH_3C_6H_4$;

R^6 is selected independently from the group consitsitng of CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$ or NO_2;

R^7 is selected independently from the group consitsitng of H, CH_3 of Ph; and

X represents halo group.

In an embodiment of the present invention, the polar aprotic solvent is preferably DMF.

In yet another embodiment of the present invention, the halo group is preferably bromo.

In yet another embodiment of the present invention, representative compound of formula (A) comprising:

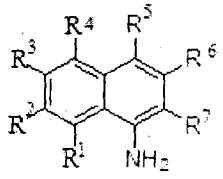
Ethyl 1-aminonaphthalene-2-carboxylate;

Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate;
Ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate;
Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate;
Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate;
Ethyl 1-amino-6-methylnaphthalene-2-carboxylate;
Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate;
Ethyl 1-amino-6-nitronaphthalene-2-carboxylate;
Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate;
Ethyl 1-amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate and;
Ethyl 1- aminophenanthrene-2-carboxylate.

In yet another embodiment of the present invention, compound of formula (B) is selected from the group consisting of
ethyl 4-(2-halo-4,5-dimethoxyphenyl)but-2-enoate,
1-(2-bromo-4,5-dimethoxyphenyl)but-2-ene derivatives,
1-(2-bromo-3,4,5,6-substituted phenyl)but-2-ene compounds.

In yet another embodiment of the present invention, the preparation of substituted naphthalene amino esters of formula (A) and their structural analogues comprising subjecting the 4-(2-halophenyl)-2-butenoates of formula (B) to intramolecular cascade cyano ene reaction in the presence of CuCN in DMF under reflux condition.

In an embodiment, present invention provides a compound of formula (A)



formula A

Wherein,

R^1, R^2, R^3, R^4 are selected independently from hydrogen, alkyl, alkoxy, halo, NO_2, CN;

R^5 is slected independently from H, CH_3, C_2H_5, Ph, $CH_3C_6H_4$;

R^6 is selected independently from CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$, NO_2 and

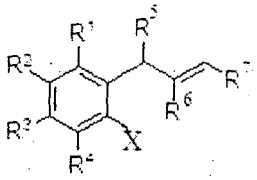
R^7 is selected independently from H, CH_3, Ph.

In yet another embodiment of the present invention, representative compounds of formula A comprising:

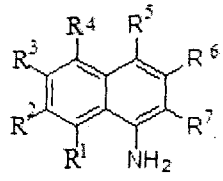
i. Ethyl 1-aminonaphthalene-2-carboxylate;
ii. Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate;
iii. Ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate;
iv. Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate;
v. Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate;
vi. Ethyl 1-amino-6-methylnaphthalene-2-carboxylate;
vii. Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate;
viii. Ethyl 1-amino-6-nitronaphthalene-2-carboxylate;
ix. Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate;
x. Ethyl 1-amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate;
xi. Ethyl 1-aminophenanthrene-2-carboxylate.

DETAILED DESCRIPTION OF THE INVENTION

Present invention provides a facile, cost-effective method involving one-pot CuCN-mediated cyano ene reaction of the compound of formula (B) for the construction of a wide variety of 1-Amino-2-naphthalenecarboxylic acid derivatives of formula (A) and their structural analogues that proceeds with high yields in a single step *via* intramolecular cascade cyano ene reaction.



Formula (B)



Formula (A)

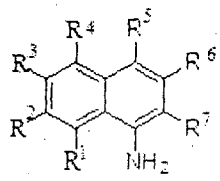
where, R^1 to R^7 and X is described herein below.

CuCN is very cheap, easy to perform at higher scales, showed remarkably broad substrate scope and good functional group tolerance and not much effluent is generated.

The one-pot CuCN-mediated cyano ene reaction typically requires substantially similar conditions of Rosenmund-von Braun Reaction. This novel transformation involves cascade reaction sequence, first substitution of bromo with CN and followed by an intramolecular cyano ene reaction to access 1-Amino-2-

naphthalenecarboxylic acid derivatives with quantitative yields. The procedure tolerates a series of functional groups, such as methoxyl, fluoro and chloro groups. Otherwise synthesis of 1-Amino-2-naphthalenecarboxylic acid derivatives requires multiple steps.

In an aspect of the invention, 1-Amino-2-naphthalenecarboxylic acid derivatives of formula (A) is represented as enlisted herein.



Formula (A)

Wherein

R^1, R^2, R^3, R^4 are selected independently from the group consitsitng of hydrogen, alkyl, alkoxy, halo, NO_2 or CN;

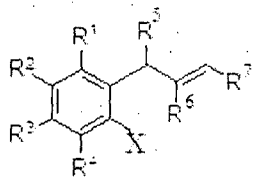
R^5 is slected independently from the group consitsitng of H, CH_3, C_2H_5, Ph or $CH_3C_6H_4$;

R^6 is selected independently from the group consitsitng of CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$ or NO_2;

R^7 is selected independently from the group consitsitng of H, CH_3 of Ph; and

X represents halo group.

Present invention provides a one pot synthesis of various 1-Amino-2-naphthalenecarboxylic acid derivatives of formula (A) and their structural analogues which includes reacting a compound of formula (B) with CuCN in polar aprotic solvent and refluxing the mixture at a temperature in the range of 145-155°C for 10-12 hours. The compound of formula (B) is



Formula (B)

wherein

R^1, R^2, R^3, R^4 are selected independently from the group consitsitng of hydrogen, alkyl, alkoxy, halo, NO_2 or CN;

R^5 is slected independently from the group consitsitng of H, CH_3, C_2H_5, Ph or $CH_3C_6H_4$;

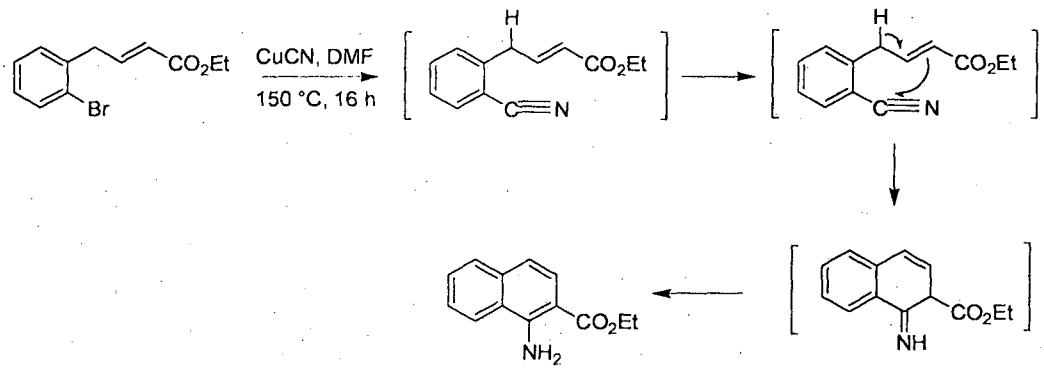
R^6 is selected independently from the group consitsitng of CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$ or NO_2;

R^7 is selected independently from the group consitsitng of H, CH_3 of Ph; and

X represents halo group.

The proposed mechanism is depicted in scheme 2 below:

Scheme 2

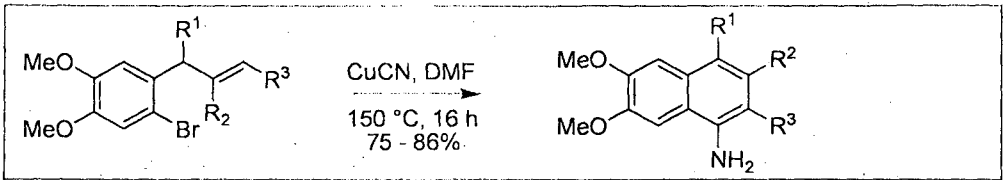


The process steps involve tandem reaction sequence where in the first step substitution of bromo with CN and followed by an intramolecular cyano ene reaction to access 1-Amino-2-naphthalenecarboxylic acid derivatives with quantitative yields. The halo group is preferably bromo. The polar aprotic solvent is selected preferably DMF.

In another embodiment, 1-(2-bromo-4,5-dimethoxyphenyl)but-2-ene derivatives are subjected to one-pot CuCN-mediated cyano ene reaction to obtain corresponding 6,7-dimethoxy-1-aminonaphthalene-3-substituted compounds in good yield. The reaction of the present invention may be carried out at 120 to 160°C in DMF for a period of 10 to 20hrs to achieve the product in good yields in the range of 75 to 90%. The products may be isolated using column chromatography and further may be purified by crystallization techniques known in the art.

The synthesis of 6,7-dimethoxy-1-aminonaphthalene-3-substituted compounds starting from 1-(2-bromo-4,5-dimethoxyphenyl)but-2-ene derivatives are depicted below in table 1.

Table 1:



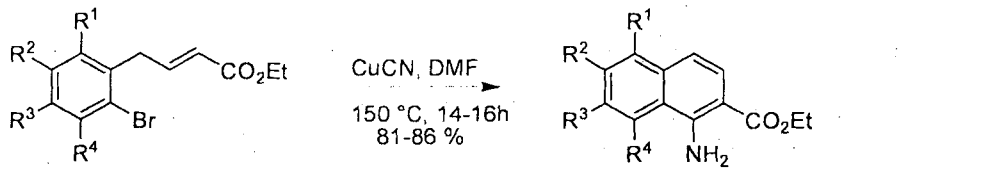
Entry	R^1	R^2	R^3	Yield (%)[a]
1	H	CO_2Et	H	86
2	H	CO_2Me	H	86
3	H	CO_2Ph	H	78
4	H	COMe	H	76
5	H	COPh	H	78
6	H	SO_2Ph	H	75
7	H	NO_2	H	76
8	H	$CONH_2$	H	82
9	Ph	CO_2Et	H	79
10	CH_3	CO_2Et	H	75
11	C_2H_5	CO_2Et	H	78
12	$CH_3C_6H_4$	CO_2Et	H	78
13	H	CO_2Et	CH_3	82
14	H	CO_2Et	Ph	78
15	H	CN	Ph	82
16	H	NO_2	CH_3	80

[a] Isolated yield after column chromatographic purification.

1-(2-bromo-3,4,5,6-substituted phenyl)but-2-ene compounds are subjected to one-pot CuCN-mediated cyano ene reaction to obtain 5,6,7,8-substituted ethyl 1-aminonaphthalene-2-carboxylate compounds in good yield. The reaction of the present invention can be carried out at 120 to 160°C in DMF for a period of 10 to 20hrs to achieve the product in good yields in the range of 75 to 90%. The products may be isolated using column chromatography and further may be purified by crystallization techniques known in the art.

The synthesis of 5,6,7,8-substituted ethyl 1-aminonaphthalene-2-carboxylate compounds starting from 1-(2-bromo-3,4,5,6-substituted phenyl)but-2-ene compounds are depicted below in table 2.

Table 2:

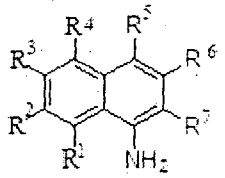


S.No	R^1	R^2	R^3	R^4	Yield (%)[a]

1	H	H	H	H	86
2	H	OMe	H	H	86
3	H	OMe	OMe	H	85
4	H	H	OMe	OMe	83
5	H	OMe	OMe	OMe	83
6	H	OMe	OMe	OMe	84
7	H	OTs	OMe	H	83
8	H	OBn	OMe	H	83
9	H	H	H	F	82
10	H	NO_2	H	H	82
11	H	CN	H	H	81
12	OMe	OMe	H	H	83
13	H	Me	Me	H	83
14	H	Me	H	H	82
15	H	Cl	H	H	81
16	H	H	H	OMe	82
17	H		-O-CH_2-O-	H	85
18	(E)-ethyl 3-(1-cyanonaphthalen-2-yl)acrylate				84
19	3-(1-hydroxybut-3-enyl)pyridine-2-carbonitrile				81
20	1-(3-bromofuran-2-yl)but-3-en-1-ol				81

[a]Isolated yield after column chromatographic purification.

In another preferred embodiment, the present invention discloses compound of formula A



Formula A

Wherein,

R^1, R^2, R^3, R^4 are selected independently from hydrogen, alkyl, alkoxy, halo, NO_2, CN;

R^5 is slected independently from H, CH_3, C_2H_5, Ph, $CH_3C_6H_4$;

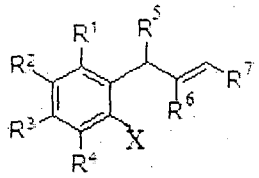
R^6 is selected independently from CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$, NO_2 and

R^7 is selected independently from H, CH_3, Ph.

1-Amino-2-naphthalenecarboxylic acid derivatives of formula (A) according to the invention encompasses Ethyl 1-aminonaphthalene-2-carboxylate, Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate, Ethyl 1-amino-6,7-

dimethoxynaphthalene-2-carboxylate, Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate, Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate, Ethyl 1-amino-6-methylnaphthalene-2-carboxylate, Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate, Ethyl 1-amino-6-nitronaphthalene-2-carboxylate, Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate, Ethyl 1-amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate, Ethyl 1- aminophenanthrene-2-carboxylate.

Present invention discloses compound of formula B



Formula B

wherein

R^1, R^2, R^3, R^4 are selected independently from hydrogen, alkyl, alkoxy, halo, NO_2, CN;

R^5 is slected independently from H, CH_3, C_2H_5, Ph, $CH_3C_6H_4$;

R^6 is selected independently from CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$, NO_2;

R^7 is selected independently from H, CH_3, Ph; and

X represents halo group.

The compound of formula (B) according to the invention, is selected from the group consisting of

ethyl 4-(2-halo-4,5-dimethoxyphenyl)but-2-enoate,

1-(2-bromo-4,5-dimethoxyphenyl)but-2-ene derivatives,

1-(2-bromo-3,4,5,6-substituted phenyl)but-2-ene compounds.

EXAMPLES

The following examples are given by way of illustration and therefore should not be construed to limit the scope of the present invention.

Example 1

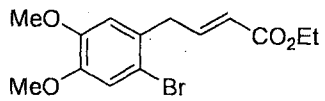
Typical Procedure for preparation of 1-Amino-2-naphthalenecarboxylic acid derivatives of formula (A)

To a stirred solution of compound of formula (B) (1 mmol) in DMF (10 mL), CuCN (3 mmol) was added and refluxed under N_2 atmosphere for 16 h (monitored by TLC). The reaction mixture was cooled to room temperature (20 to 40°C), then diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which was purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: EtOAc (70:30) as an eluent] gave 1-Amino-2-naphthalenecarboxylic acid derivatives in 86% yield.

The product, 1-Amino-2-naphthalenecarboxylic acid derivatives compound of formula (A) is characterized and compared with compound of formula (B) by IR, ^1H NMR, ^{13}C NMR and elemental analysis. As shown below:

Example 2

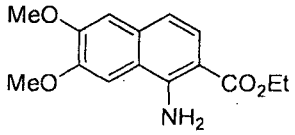
Characterization of Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)but-2-enoate:



Yield: 86%, IR ($CHCl_3$): 765, 784, 1031, 1184, 1318, 1447, 1480, 1594, 1640, 1712, 2225, 2938, 2983 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J = 7.22 Hz, 3H), 3.57 (dd, J = 1.75, 6.48 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.18 (q, J = 7.22 Hz, 2H), 5.74 (dt, J = 1.75, 15.52 Hz, 1H), 6.66 (s, 1H), 6.96-7.10 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.10, 38.07, 55.81, 55.89, 60.01, 113.03, 114.19, 115.47, 122.37, 128.85, 145.50, 148.39, 165.98; Analysis: $C_{14}H_{17}BrO_4$ requires C 51.08, H 5.21 found C 50.96, H 5.17%.

Example 3

Characterization of ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate:

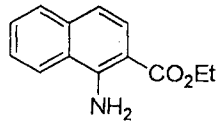


Yield: 85%, IR ($CHCl_3$): 756, 792, 1013, 1181, 1325, 1474, 1480, 1549, 1640, 2983, 2398, 2420 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (t, J = 7.10 Hz, 3H), 4.00 (s,

3H), 4.01 (s, 3H), 4.36 (q, J = 7.10 Hz, 2H), 6.32 (brs, 1H), 6.94 (d, J = 8.86 Hz, 1H), 7.02 (s, 1H), 7.08 (s, 1H), 7.78 (d, J = 8.86 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ 14.36, 55.59, 55.69, 59.97, 101.18, 103.83, 107.09, 114.84, 117.66, 125.18, 132.45, 147.64, 148.60, 150.92, 168.84; **Analysis:** $C_{15}H_{17}NO_4$ requires C 65.44, H 6.22, N 5.09 found C 65.38, H 6.16, N 4.97%.

Example 4

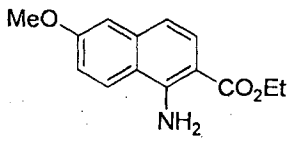
Ethyl 1-aminonaphthalene-2-carboxylate



Yield: 85%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 798, 865, 964, 1015, 1135, 1157, 1232, 1264, 1471, 1665, 2965, 3335, 3346; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.36 (q, J = 7.1 Hz, 2H), 7.05 (d, J = 8.9 Hz, 1H), 7.40-7.56 (m, 2H), 7.72 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.9 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.1, 104.2, 115.7, 121.4, 123.1, 125.0, 126.6, 128.2, 128.4, 136.4, 148.8, 168.8; **Analysis:** $C_{13}H_{13}NO_2$ requires C, 72.54 ; H, 6.09 ; N, 6.51; found: C, 73.08; H, 6.34; N, 6.67 %.

Example 5

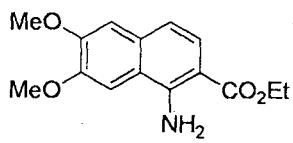
Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate



Yield: 78%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 870, 1076, 1245, 1340, 1599, 1672, 3346, 3457; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.0 Hz), 4.35 (q, J = 7.0 Hz, 2H), 6.05 (s, 2H), 6.90 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 7.16 (s, 1H), 7.75 (d, J = 9.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.5, 55.2, 60.0, 103.1, 107.0, 115.0, 118.0, 123.2, 127.5, 138.3, 148.9, 159.5, 168.8; HRMS (ESI+, m/z): calcd for $(C_{14}H_{15}NO_3)^+$ [$(M+Na)^+$] 268.0944; found: 268.0938; **Analysis:** $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71; found: C, 68.18; H, 5.99; N, 5.45 %.

Example 6

Ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate

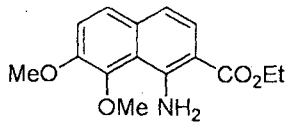


Yield: 74%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 798, 865, 964, 1015, 1135, 1157, 1232, 1264, 1471, 1665, 2965, 3335, 3346; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.36 (q, 2H, J = 7.1 Hz), 7.05 (d, J = 8.9 Hz, 1H), 7.40-7.56 (m, 2H), 7.72 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.9 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.1, 104.2, 115.7, 121.4, 123.1, 125.0, 126.6, 128.2, 128.4, 136.4, 148.8,

168.8; **Analysis:** $C_{15}H_{17}NO_4$ requires C, 65.44 ; H, 6.22 ; N, 5.09 found: C, 65.69 ; H, 6.18 ; N, 5.11%.

Example 7

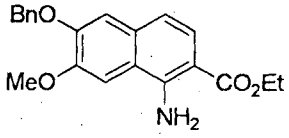
Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate



Yield: 73%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 779, 826, 956, 1018, 1267, 1579, 1672, 3334, 3464; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.2 Hz, 3H), 3.97 (s, 6H), 4.35 (q, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 10.4 Hz, 1H), 7.24-7.28 (m, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.2, 56.6, 59.6, 61.2, 102.5, 113.8, 116.6, 117.8, 124.2, 125.1, 132.9, 146.8, 148.4, 150.9, 168.6; **Analysis:** $C_{15}H_{17}NO_4$ requires C, 65.44 ; H, 6.22 ; N, 5.09 found: C, 65.34 ; H, 6.31 ; N, 5.12%.

Example 8

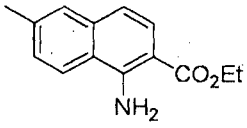
Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate



Yield: 76%; Colorless solid; **mp:** 144-145°C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1247, 1483, 1619, 1676, 3434, 3452; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.1 Hz, 3H), 4.00 (s, 3H), 4.35 (q, 2H, *J* = 7.1 Hz), 5.26 (s, 2H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 7.18 (s, 1H), 7.30-7.51 (m, 6H), 7.76 (d, *J* = 8.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.5, 55.8, 60.1, 71.3, 104.3, 107.6, 115.2, 117.9, 125.5, 127.4, 128.1, 128.7, 132.9, 1136.7, 147.5, 147.9, 151.8, 168.9; **Analysis:** $C_{21}H_{21}NO_4$ requires C, 71.68; H, 6.02; N, 3.99; found: C, 71.63; H, 5.95; N, 3.89%.

Example 9

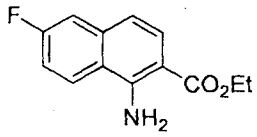
Ethyl 1-amino-6-methylnaphthalene-2-carboxylate



Yield: 81%; Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1078, 1222, 1239, 1257 1605, 1663, 3352, 3453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 2.55 (s, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.5, 22.0, 60.2, 104.9, 116.1, 120.9, 123.4, 125.7, 128.4, 130.4, 134.6, 134.9, 147.9, 168.9; HRMS (ESI+, *m/z*): calcd for $(C_{14}H_{15}NO_2)^+$ [$(M+Na)^+$] 252.0995; found: 252.0989; **Analysis:** $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11; found: C, 73.26; H, 6.52; N, 6.01%.

Example 10

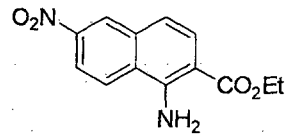
Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate



Yield: 88%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 767, 1249, 1604, 1673, 2987, 3347, 3447; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.1 Hz, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 7.15-7.24 (m, 1H), 7.34 (dd, *J* = 2.5, 7.1 Hz, 1H), 7.84-7.92 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.5, 62.3, 104.1, 111.9, 114.9, 120.0, 124.3, 128.1, 138.1, 148.8, 161.1, 163.6, 168.7; **HRMS** (ESI+, *m/z*): calcd for $(C_{13}H_{12}FNO_2)^+$ [(M+Na)$^+$] 256.0744; found: 256.0730; **Analysis:** $C_{13}H_{12}FNO_2$ requires C, 66.94; H, 5.19; N, 6.01; found: C, 67.03; H, 5.13; N, 5.89%.

Example 11

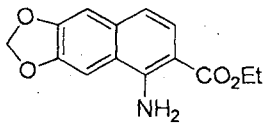
Ethyl 1-amino-6-nitronaphthalene-2-carboxylate



Yield: 91%; Red solid; **mp:** 176-177°C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.0 Hz, 3H), 4.41 (q, *J* = 7.0 Hz, 2H), 6.90 (s, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 8.02 (t, *J* = 8.8 Hz, 1H), 8.18 (d, *J* = 2.26 Hz, 1H), 8.20 (d, *J* = 2.26, 1H), 8.64 (d, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.7, 107.1, 116.8, 118.2, 123.4, 124.4, 125.6, 129.0, 135.6, 147.0, 148.2, 168.2; **HRMS** (ESI+, *m/z*): calcd for $(C_{13}H_{12}N_2O_4)^+$ [(M+Na)$^+$] 283.0689; found: 283.0682; **Analysis:** $C_{13}H_{12}N_2O_4$ requires C, 60.00; H, 4.65; N, 10.76; found: C, 59.95; H, 4.51; N, 10.65%.

Example 12

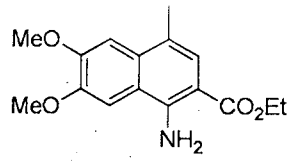
Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate



Yield: 82%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 3.92 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 7.02-7.11 (m, 2H), 7.82 (t, *J* = 8.8 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 60.0, 98.7, 101.3, 104.5, 104.9, 115.6, 119.0, 125.5, 134.0, 147.4, 147.8, 149.2, 168.8; **Analysis:** $C_{13}H_{12}N_2O_4$ requires C, 64.86; H, 5.05; N, 5.40; found: C, 64.79; H, 5.12; N, 5.46%.

Example 13

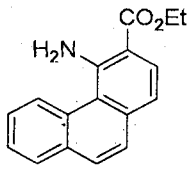
Ethyl 1-amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate



Yield: 81%; Yellow solid; **mp:** 135-136°C; **IR** ($CHCl_3$, cm^{-1}): u_{max} 798, 865, 964, 1063, 1205, 1232, 1250, 1462, 1482, 1513, 1602, 1674, 2980, 3352, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (t, *J* = 7.07 Hz, 3H), 2.50 (s, 3H), 4.02 (s, 6H), 4.32 (q, 2H, *J* = 7.07 Hz), 7.11 (s, , 1H), 7.13 (s, 1H), 7.62 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.3, 18.9, 55.3, 55.4, 59.8, 101.7, 103.5, 103.6, 118.1, 120.1, 131.5, 146.3, 148.0, 150.5, 168.7 ; **Analysis:** $C_{16}H_{19}NO_4$ requires C, 66.42 ; H, 6.62 ; N, 4.84; found: C, 66.42 ; H, 6.38 ; N, 4.48%.

Example 14

Ethyl 1- aminophenanthrene-2-carboxylate



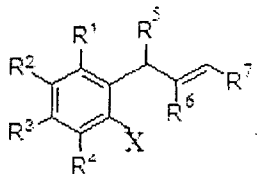
Yield: 71%; Yellow oil; **IR** ($CHCl_3$, cm^{-1}): u_{max} 791, 845, 964, 1052, 1215, 1239, 1240, 1412, 1472, 1533, 1664, 2970, 3332, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (t, *J* = 7.07 Hz, 3H), 4.34 (q, 2H, *J* = 7.07 Hz), 7.09 (d, J = 8.59 , 1H), 7.49-7.64 (m, 1H), 7.70-7.75 (d, J = 8.71, 1H), 7.86 (d, J = 8.96, 1H), 8.03 (d, J = 8.47, 1H), 9.17 (d, J = 8.21, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.4, 16.4, 108.2, 116.7, 119.1, 124.5, 125.6, 126.5, 127.0, 128.3, 129.1, 129.6, 130.8, 132.8, 137.1, 151.0, 169.1; **Analysis:** $C_{17}H_{15}NO_2$ requires C, 76.96 ; H, 5.70 ; N, 5.28; found: requires C, 76.71 ; H, 5.51 ; N, 5.22

ADVANTAGES OF THE INVENTION

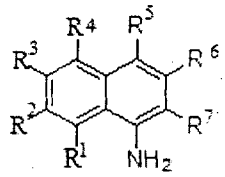
1. One pot process with good yields obtained
2. Avoids hazardous chemicals

The Claims:

1. A one pot process for the preparation of compound of formula (A) and their structural analogues comprising reacting compound of formula (B) with CuCN in solvent at a temperature in the range of 145°-155°C for period in the range of 10 to12 hours;



Formula (B)



Formula (A)

Wherein,

R^1, R^2, R^3, R^4 are selected independently from the group consitsitng of hydrogen, alkyl, alkoxy, halo, NO_2 or CN;

R^5 is slected independently from the group consitsitng of H, CH_3, C_2H_5, Ph or $CH_3C_6H_4$;

R^6 is selected independently from the group consitsitng of CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$ or NO_2;

R^7 is selected independently from the group consitsitng of H, CH_3 of Ph; and

X represents halo group.

2. The process according to claim 1, wherein the solvent used is polar aprotic solvent.
3. The process according to claim 2, wherein the solvent used is preferably DMF.
4. The process according to claim 1, wherein the halo group is preferably bromo.
5. The process according to claim 1, wherein yiled of the compound of formula A is ranging between 75 to 90%.
6. The process according to claim 1, wherein representative compound of formula (A) comprising:

Ethyl 1-aminonaphthalene-2-carboxylate;

Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate;

Ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate;

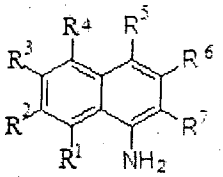
Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate;

Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate;
Ethyl 1-amino-6-methylnaphthalene-2-carboxylate;
Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate;
Ethyl 1-amino-6-nitronaphthalene-2-carboxylate;
Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate;
Ethyl 1-amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate and;
Ethyl 1-aminophenanthrene-2-carboxylate.

7. The process according to claim 1, wherein, compound of formula (B) is selected from the group consisting of
ethyl 4-(2-halo-4,5-dimethoxyphenyl)but-2-enoate,
1-(2-bromo-4,5-dimethoxyphenyl)but-2-ene derivatives,
1-(2-bromo-3,4,5,6-substituted phenyl)but-2-ene compounds.

8. The process according to claim 1, wherein the preparation of substituted naphthalene amino esters of formula (A) and their structural analogues comprising subjecting the 4-(2-halophenyl)-2-butenoates of formula (B) to intramolecular cascade cyano ene reaction in the presence of CuCN in DMF under reflux condition.

9. A compound of formula (A)



formula A
Wherein,
R^1, R^2, R^3, R^4 are selected independently from hydrogen,
alkyl, alkoxy, halo, NO_2, CN;
R^5 is slected independently from H, CH_3, C_2H_5, Ph, $CH_3C_6H_4$;
R^6 is selected independently from CO_2Et, CO_2Me, CO_2Ph, COMe, COPh, CN, SO_2Ph, $CONH_2$, NO_2 and
R^7 is selected independently from H, CH_3, Ph.

10. The compound of formula A according to claim 7, representative compounds of formula A comprising:
i. Ethyl 1-aminonaphthalene-2-carboxylate;

ii. Ethyl 1-amino-6-methoxynaphthalene-2-carboxylate;
iii. Ethyl 1-amino-6,7-dimethoxynaphthalene-2-carboxylate;
iv. Ethyl 1-amino-7,8-dimethoxynaphthalene-2-carboxylate;
v. Ethyl 1-amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate;
vi. Ethyl 1-amino-6-methylnaphthalene-2-carboxylate;
vii. Ethyl 1-amino-6-fluoronaphthalene-2-carboxylate;
viii. Ethyl 1-amino-6-nitronaphthalene-2-carboxylate;
ix. Ethyl 5-aminonaphtho[2,3-d][1,3]dioxole-6-carboxylate;
x. Ethyl 1-amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate;
xi. Ethyl 1-aminophenanthrene-2-carboxylate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2013/000019

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C227/12 C07C229/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAZUHIRO KOBAYASHI ET AL.: "Efficient Synthesis of 1-Amino-2-naphthalenecarboxylic Acid Derivatives via a Sequential Michael Addition/Enolate-Nitrile Coupling Route and Its Application to Facile Preparation of 9-Amino Analogues of Arylnaphthofuranone Lignans", JOURNAL ORGANIC CHEMISTRY, vol. 62, no. 3, 1997, pages 664-668, XP002696277,	10
Y	page 665, Scheme I, compound 6; page 666,	9
A	Table 1, entries for 6b, 6c, 6f, 6j and from page 666 to page 668 the corresponding "Experimental Section"	1-8
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2013	14/05/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2013/000019

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/059773 A1 (MERCK SHARP & DOHME [US]; KUDUK SCOTT D [US]; BESHORE DOUGLAS C [US];) 27 May 2010 (2010-05-27)	10
Y	page 31, Scheme 1, compound 4	9
A		1-8

X	BRUNCKO M ET AL: "Naphthamidine urokinase plasminogen activator inhibitors with improved pharmacokinetic properties", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 15, no. 1, 3 January 2005 (2005-01-03), pages 93-98, XP027800857, ISSN: 0960-894X [retrieved on 2005-01-03]	9
A	page 95, compound 5d	1-8,10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2013/000019

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		DO P2011000135 A	31-07-2011
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		PT 2358686 E	06-12-2012
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		SV 2011003912 A	13-10-2011
		US 2011224198 A1	15-09-2011
		WO 2010059773 A1	27-05-2010